REVIEW

Straightening out Peyronie's: a medical and surgical approach to the patient

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Purpose: *Peyronie's disease is characterized by plaque formation within the tunica albuginea of the penile corpora cavernosa. The exact etiology of Peyronie's is uncertain at this time, and multiple treatment options exist. Following a literature review, a treatment algorithm has been developed to streamline decisions for both medical and surgical intervention.*
Methods: *A review of the Medline literature published between 1940 and 2008 was performed looking at the history, pathophysiology, medical and surgical treatments for Peyronie's disease.*
Results: *The current standard is to treat Peyronie's with expectant medical management or by adding oral, topical, or injected medicines to the plaque until the process is stabile for 12 months. Besides pain relief, few patients experience significant disease regression with nonsurgical interventions. Although initially discouraging, recent studies looking at plaque injection with verapamil, interferon, or collagenase show promising objective improvements. Patients with disabling curvature in the chronic disease phase respond best to surgical intervention. A review of the mechanisms, adverse effects, and supporting literature are provided.*
Conclusion: *The approach to Peyronie's disease should begin with understanding patient expectations and making them aware of risks and benefits of each treatment option. Medical treatments provide a reasonable starting point since they: lessen pain in most, improve deformity in some, but completely resolve symptoms in only a few. Those who fail to experience adequate improvement with medical therapy, and those with stable yet significant deformity, should proceed to surgical intervention. The algorithm developed in this review provides an organized approach for making decisions about patient treatment.*

Key Words: Peyronie's, indurato penis plastica, review, medical treatment, surgical treatment, treatment algorithm

Introduction

Peyronie's disease was first reported by Fallopius in 1561, but was not "popularized" until 1743 by the surgeon of King Louis XV of France, Francois Gigot de la Peyronie. Peyronie initially recommended treatment with Barege spa water and mercurial ointments.

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Peyronie's disease is the result of plaque formation within the tunica albuginea. The resulting curvature may result in painful erections and difficulty with intercourse. For those with minimal plaque and mild curvature, reassurance that the condition is benign may be all the patient needs. However, most patients will opt for some form of medical management. A subset of patients who are afflicted with a disabling deformity may find the best treatment option to be surgery.[1] Goals for each intervention include relieving pain, minimizing deformity, and restoring erectile function. In light of recent advancements, and the lack of well-controlled prospective studies,

the time has come for a consensus statement to clarify and streamline an effective treatment algorithm for Peyronie's disease.

Epidemiology

Peyronie's is uncommon, occurring only in up to 3.2%[2] of Caucasian men, while rarely affecting African-American men. Since corporal elasticity diminishes with age, it is understandable that most men who seek medical attention do so later in life, typically in their fifth decade. However, a wide age range (20 to 83 years) has been reported with only 8.2% of men presenting younger than 40 years.[3] Correlates to Peyronie's have included Dupuytren's contractures, plantar fascial contractures (Lederhose's disease), tympanosclerosis, trauma, urethral instrumentation, diabetes, gout, Paget's disease, and even the use of beta-blockers.[4]

Genetic influences may also be involved. A familial pattern of inheritance has been associated with both HLA-B7 antigens and Dupuytren's contractures.[5,6] Other studies have shown associations with tissue types HLA-B27, HLA-A1, HLA-DQw2, and HLA-DQ5.[6-8] Although these HLA associations initially spurred an interest in the possibility of autoimmune or infectious etiologies, no compelling evidence for either process has been demonstrated.

Although the epidemiology of this disease is unlikely to be changing, some experts believe that the clinical incidence of Peyronie's is increasing.[9] A possible explanation could be related to the recent increased awareness of sexual dysfunction, and the emergence of more effective treatment options.

Etiology

Peyronie's is a disease process that primarily involves the tunica albuginea. The etiology of the inflammatory response that results in the offending plaque is not fully understood. The most plausible theory is that stretch-and-bend trauma, occurring during sexual intercourse, results in tunical delamination.[10] Delamination not only incites inflammation, induration, and fibrin deposition, but also activates fibroblasts and leukocyte reactions.[11] Such studies have implicated platelets from tunical hematomas, as the pivotal cause for plaque formation. These platelets release fibrin, which contributes to scar formation. Additionally, the release of serotonin, platelet-derived growth factors, and transforming growth factors has been implicated in the process. Clearance of these factors may be impeded by the avascular nature of the tunica albuginea. In particular, the build up of TGF-β results in inflammatory responses by binding to cell surface receptors, activating connective tissue synthesis while inhibiting collagenases, ultimately slowing scar resorption.[12,13] Thus TGF-β can lead to an ongoing inflammatory process.[9] The predominance of type III collagen in the Peyronie's scar render them particularly prone to contraction. The replacement of elastic tunica with rigid and contraction- inducing type III collagen often leads to erectile dysfunction.

Peyronie's disease and erectile dysfunction

The reported incidence of erectile dysfunction (ED) with Peyronie's disease varies due to the plethora of ED-related co-morbidities found with this age group. Although some see ED as a late-developing feature, the overall risk for Peyronie's-specific ED, at any age, is 30%.[9,14] ED in this setting is often attributed to venous leakage from reduced tunical compliance, a result of type III collagen replacing the normally compliant elastic fibers. This rigid segment of tunica is unable to occlude effluxing venous cavernosal blood, resulting in a segmental venous leak and detumescense—a process labeled "veno-occlusive dysfunction." On the other hand, not all of Peyronie's-related ED can be explained by venous dysfunction. Lopez and Jarow studied 76 patients and found 41% of this sample had arterial disease.[15] Additionally, performance anxiety related to the presence of the physical abnormality may further worsen erectile function.[16]

Clinical presentation

Most patients present with concerns about a penile lump, curvature, or painful erections. Excluding congenital chordee, dorsal vein thrombosis, infiltrative cancer, or a sexually transmitted disease will assist in making the Peyronie's diagnosis. As part of the initial workup, it is important to record plaque dimensions, degree of penile curvature, the presence of ED, duration of disease, and perception of pain. Plaque dimensions may often be defined with the aid of ultrasound imaging. In patients contemplating surgery, anterior-posterior and lateral photographs are useful to document the degree and location of curvature.

Medical management

Treating Peyronie's should begin with educating the patient and his partner concerning the typical disease timeline and its varied degrees of progression. The

disease process begins with an acute inflammatory phase, followed by gradual resolution of pain and plaque remodeling. During the subsequent chronic phase, plaque size and penile curvature stabilize. For some men with minimal symptoms, reassurance may be all that is required. Although a spontaneous plaque resolution rate of up to 13% has been reported, most patients opt for some form of treatment.[17] The observation that most dramatic improvements are seen in those treated in the early-stage of their disease, have led most to recommend early medical intervention.[11]

There is no single definitive medical therapy for Peyronie's disease. Patients with evolving or changing plaque should continue medical therapy until their disease has stabilized. Treatment options for patients in the acute phase include: (1) oral therapy, (2) injection therapy, (3) energy transfer, and (4) topical treatments.

Oral therapy

Vitamin E: 800-1000 I.U. daily in divided doses

Scardino and Scott first reported the antioxidant effects of Vitamin E in 1948. In uncontrolled trials, they observed a 78% decrease in curvature and a 91% reduction in plaque size when patients were given Vitamin E.[18] More recently, at a 1993 NIH conference on Peyronie's disease, Devine and Snow reported a 99% reduction in pain but only a subjective 13% reduction in curvature in 105 men taking vitamin E. Low cost and excellent tolerability continue to make this agent a popular treatment modality, particularly for the reduction of pain.

Colchicine: 0.6 mg PO 2x-3x daily for 3 months

Colchicine has the unique ability to reduce collagen synthesis by either interfering with transcellular movement of protocollagen, or by increasing collagenase activity leading to plaque breakdown.[19,20] In addition, colchicine acts to reduce the inflammatory response by inhibiting leukocyte adhesion and motility, inhibiting cellular mitosis, and blocking the lipoxygenase pathway of arachidonic acid metabolism.

Although earlier studies demonstrated a 26% decrease in curvature and a 50% reduction in plaque size,[21] a more recent randomized placebo-controlled study found no significant difference between placebo and colchicine in regards to objective outcomes.[22] Although colchicine is generally well tolerated, up to one-third of men can experience diarrhea.

Potassium aminobenzoate (Potaba): 12 gm-20 gm PO daily for 3 months

In 1959, Zarafonetis and Horrax reported Potaba as a successful Peyronie's treatment.[23] In their original study of 21 patients, 100% reported less pain, 82% experienced a reduction in curvature, and 76% had resolution of their plaque. In a recent randomized, prospective placebo-controlled study, Potaba showed some protective effect on the progression of penile curvature, however no significant reductions in curvature or plaque size were significant between control and treatment groups.[24]

Although Potaba's mechanism of action is poorly understood, it is thought that a reduction in fibrogenesis occurs as a result of local reduction of serotonin levels. The reduction in fibrogenesis is accomplished by increased oxygenation of tissues and increased monoamine oxidase activity. Excitement about Potaba's efficacy is tempered by its relative high cost and gastrointestinal side effects.

Tamoxifen: 20 mg PO 2X daily for 3 months

Tamoxifen is a non-steroidal anti-estrogen that affects the inflammatory response by facilitating release of TGF-β from fibroblasts. Tamoxifen has been shown to stimulate release of TGF-β from fetal fibroblasts, which in small amounts may reduce inflammatory responses, fibroblast production, and angiogenesis.[25] Lack of long term data limits the reliability of this treatment option.

Injection therapy

Verapamil: intralesional injection, 5 mg-10 mg every other week, 12 injections

In 1994, Levine was the first to suggest intralesional injections of a calcium channel blocker to treat Peyronie's.[26] Conceptually, this was an extension of bench research demonstrating that verapamil could slow scar formation by both the induction of collagenase activity and by blocking calcium-dependent mechanisms by which fibroblasts deposit collagen.[27] Although Steriger et al found verapamil to have no significant effect when compared to placebo in a randomized double-blinded placebo-controlled study,[28] a recent study demonstrated stabilization of plaque in 73 of 94 patients.[29] Early studies also suggest best results have been seen in men with small (< 4 cm) non-calcified plaques with an angulation of less than 30 degrees.[9,30] Other than ecchymosis, no other adverse events from verapamil injections have been reported.

Steroids: dexamethasone and long-acting triamcinolone

In general there is a lack of supporting evidence for steroid use as an intralesion injection. Additionally,

serious side effects, such as local tissue atrophy and tissue fibrosis, limit widespread use.[31] Of note, performing surgery after steroid injections puts the neurovascular bundle at increased risk as tissue planes become distorted as a result of steroid use.

Collagenase: intralesional injection 10,000 units 3X weekly, repeat at 3 month

The concept of intralesional injections to treat Peyronie's actually started a decade prior to verapamil injections. Walsh stated that clostridial collagenase could dissolve surgically excised plaque tissue.[32] This finding resulted in the injection of collagenase directly into the plaque of 31 men with a reported 65% reduction of curvature.[33] Subsequently, a randomized double blinded placebo control trial demonstrated a statistically significant "positive response" which was greatest in those patients with less than 30 degree deformity and plaque length less than 2 cm.[34] More recently Jordan reported statistically significant objective improvements compared to baseline in regards to penile deviation angle, plaque width and length.[35] Xiaflex, a collagenase from Auxilium Pharmaceuticals., is reported to have shown a measurable decrease in deviation angel in over half patients treated in a phase II trial, according to company website www.auxilium.com.

Interferon: 0.5-3 million units, from 3-times a week to once every other week

The concept of injecting interferon into Peyronie's plaque arose from bench research on fibroblasts. Duncan and colleagues used fibroblasts from actual penile plaque to demonstrate that interferon alpha-2b decreased both the rate of fibroblast proliferation, and the production of extra cellular collagen, while increasing the production of collagensases.[36] Four years later, Wegner was the first to report results of intralesional interferon alpha-2b with both objective and subjective improvements.[37] Since then, several clinical studies have been published with varied outcomes.[38,39] Recently, a single-blinded placebo-controlled study found 27% reduction in curvature ($p < 0.01$) and greater than 50% reduction in plaque volume ($p < 0.001$) although IIEF scores addressing ED were not significantly different.[40] Flu-like side effects, sinusitis, and arthralgia, were found to be mild and short lived.

Parathyroid hormone: 50 units every week for 8 weeks

This historical approach to treating Peyronie's was reported by Morales in 1975. Excess parathyroid hormone has been known to depress collagen synthesis and promote collagen degradation. In an early study, pain reduction occurred in most patients and a majority reported subjective decrease in curvature.[41] Few follow-up studies have been conducted exploring this treatment.

Energy transfer

Extra-corporal shock wave therapy (ESWT) 3000 shocks at an average power level 4

Several studies have looked at ESWT as a non-invasive treatment option for Peyronie's. The technique includes contrast injection directly into plaque and shock delivery using the adjacent thigh as an interface. Possible mechanisms include improved vascularization, direct effect on nociceptors or simply a decrease in collagen clumping within the plaque. Early studies, including a meta-analysis, observed improvement in sexual function and penile pain with no consistent objective improvements in plaque size or angulation.[42] However, two recent studies from Europe report decrease angulation of 35% and 33% which was statistically significant in both studies with mean follow up of 12 and 44 months respectively.[43,44]

Topical treatment

Topical verapamil cream: 15% gel topical 2X daily

As mentioned previously, calcium channel blockers may inhibit the synthesis and secretion of extracellular matrix proteins while degrading existing scar tissue by increasing collagenases. In order to simplify treatment and avoid penile injections, the effectiveness of topical verapamil was evaluated. The exact mechanism for improvement is difficult to explain given the absence of verapamil in plaques excised from patients who were initially treated with topical cream and subsequently underwent surgery.[45] Nevertheless, a randomized, placebo-controlled, double-blinded pilot study found at 9 months a 61% reduction in curvature, 84% reduction in plaque size, significant improvement in perceived erections and pain resolution in entire treatment arm.[46]

Iontophoresis: 5 mg verapamil/8 mg dexamathasone, 2.4 mA current for 20 minutes, 4X week for 6 weeks

Iontophoresis is the electrokinetic transdermal transport of charged molecules into diseased tissue by repulsive electromotive force. Use of this technology in Peyronie's has been extrapolated from successful applications

in arthritis and other soft tissue diseases. In 1995, Montorsi reported effectively treating Peyronie's by transporting dexamethasone and verapamil to the plaque using iontophoresis.[47] More recently, a prospective, randomized study compared electromotive delivery of verapamil and dexamethasone compared to 2% lidocaine (control). Although pain relief occurred in both groups, only the treatment group showed reductions in plaque size (824 mm to 348 mm) and angulation (43 to 21 degrees).[48] Although these findings were supported by an earlier study in which plaque size and penile deformity were significantly improved from baseline,[49] both studies had relatively short follow-up (4 weeks) post treatment.

Surgical treatment

In most men, medical treatment for Peyronie's will result in pain-free erections. Unfortunately, relatively few will experience significant straightening of their phallus, and will therefore, contemplate surgical intervention. It is imperative that patients understand that surgery is not a cure for the disease process. The optimal surgical candidate has progressed to the chronic disease phase with a stable, painless curvature, and has not responded to conservative measures. Additionally, excessive deformity, ED with associated hourglass deformity or hinge segment, and those with ventral deformity are also appropriate surgical patients.[50,51]

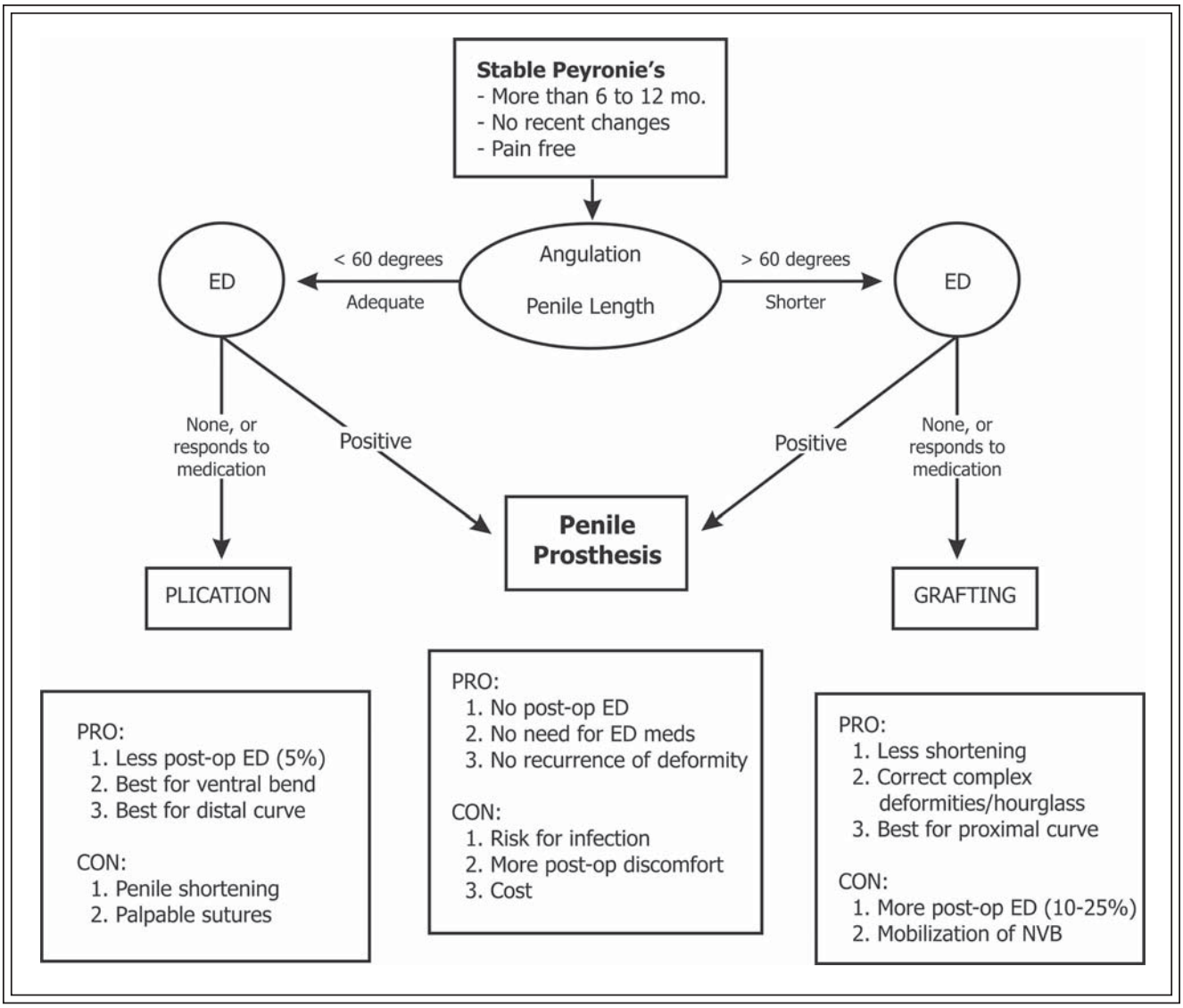

Figure 1. Treatment algorithm for Peyronie's disease.

Surgical options include: (1) penile prosthesis, (2) tunical lengthening (grafting), and (3) tunical shortening (a Nesbit-like plication). The best possible surgical outcome requires both careful patient selection and the realization that a combination of procedures is sometimes required. Figure 1 outlines the recommendations and reasonable expectations for each option. Patient preference and their willingness to accept the surgical risk associated with each procedure will often direct the surgical approach. For instance, to minimize penile shortening, some men choose a grafting procedure in spite of the increased risk for erectile dysfunction. On the other hand, those who wish to minimize the risk of erectile dysfunction will most likely choose a Nesbit-like procedure.

Penile prosthesis

A penile prosthesis is typically reserved for those patients who have both erectile dysfunction and Peyronie's. As medical treatments for ED advance, fewer patients require implantation. In general, a prosthesis can be avoided if an adequate erection can be supported by less invasive means. Fortunately, the corporal tissue underlying Peyronie's plaque is "uniformly uninvolved".[1] For this reason; most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. Cases with severe deformity may require intra-operative "modeling" of the penis over inflated cylinders.[52] When modeling alone is not fully effective, a judiciously placed incision with or without grafting may further enhance the surgical outcome.

Tunical shortening

In 1965, Nesbit described removal of tunical ellipses opposite an inelastic corporal segment to treat congenital penile curvature.[53] Fourteen years later, this technique translated into a successful treatment option for Peyronie's disease.[54] Modifications that have simplified and reduced morbidity include the transverse closure of longitudinal corporotomies[55,56] and incision-free suture-based imbrications.[57] A 16-dot placation technique, described by Gholami and Lue, uses paired tunica sutures adjacent to periurethral structures, or neurovascular bundle, to repair ventral and dorsal curvature respectively. Data from their review of 132 patients showed 93% with straight erections at 6 months, with the most common complaint being penile shortening in 41%.[58] Overall, success rates have improved with better patient selection and the addition of a non-absorbable suture to each plication site to reduce distraction failures.

TABLE 1. **Grafting materials**

Graft	Advantages	Disadvantages
Autologous tissue		
Dermis	Low infection risk, low antigenicity	Recurrent curvature 35%, contracture and shortening 40%, 17% re-operation rate at 10 yrs[66-68]
Vein *saphenous*	Good compliance, can be perfused, theoretical nitric oxide release	High post op ED, lymphocele 1%, altered penile sensation 10%, variable patient satisfaction[69,70]
Fascia lata	Tensile strength, undergoes vascular growth and endothelialization, straight post-op erections [71]	Harvest site
Tunica vaginalis	Straight erection, histologically similar to albiguinia	Contracture rate 42%, scrotal incision needed[72]
ECM tissue		
Cadaveric pericardium *most widely used*	Straight erection 88%, low incidence penile shortening, excellent strength, most popular	Poor result with lateral curvature, high incidence ED with larger graft size[65,73]
SIS *porcine jejunum*	Decrease inflammatory reaction, in-growth of endothelial cells	High postop hematoma and recurrent plaque 25%, variable penile straightening[73]
Synthetic material		
PTFE *(Gortex)*	High infection, fibrosis. Graft contracture due to inelasticity	Availability, low postop curvature[60]

The best candidate for tunical shortening will have adequate erections, a mature plaque without concomitant hourglass deformity, a curvature less than 60 degrees and adequate penile length. The most common complication of this procedure is penile shortening, which is usually not significant enough to affect sexual relations. Other adverse events include phimosis, penile narrowing, erectile dysfunction (ED), suture granuloma, and palpable suture lumps. The overall success rate for the original Nesbit procedure was 82% (n = 295),[59] with rates of 79%-95% reported for Nesbit-modifications.[55,56,60,61]

Plication techniques will remain an important treatment option for Peyronie's. From a surgeon's point of view, it is a relatively straightforward surgical procedure that also lends itself to enhancing, or "touching-up" other operative approaches. From a patient's perspective, it carries the lowest risk of post-operative ED (5%).[1]

Tunical lengthening

Replacement of diseased tunica was largely unsuccessful until Devine and Horton introduced dermal grafting in 1974.[62] Since then, an array of grafting materials has been studied. Grafting materials include autologous tissue such as temporalis fascia, dura mater, tunica vaginalis, vascularized preputial tissue, dorsal and saphenous veins, cadaveric tissues and lastly, synthetic materials such as Dacron, Gore-Tex, and silastic.[9,11] Unfortunately, no grafting material has been universally adopted as superior. A summary of frequently used grafting materials can be found in Table 1.

Additional challenges surround the concept of "complete" plaque excision. The deleterious histological effects of Peyronie's extend beyond "visibly" altered tunica vaginalis, making the goal of complete surgical excision difficult. Additionally, grafting large areas seems to have a negative effect on erectile function, resulting in ED rates as high as 25%.[1] Lastly, although initial surgical results were excellent, graft contracture and long-term failures resulted in a disappointing 17% re-operation rate.[63]

In an effort to improve complication rates, Gelbard and Hayden introduced the concept of plaque "incision" with grafting.[64] Less disruption of the tunica and its underlying erectile tissue resulted in reduced rates of postoperative erectile function.[9]

Egydio et al described the operative technique preferred at our medical center. Their use of geometric principles requires only two measurements of the angled penis, the difference of which, represents the optimal distance between the tips of a simple, "Mercedes-Benz" tunical incision.[65]

Grafting should be considered in men with a shorter phallus, more proximal plaque, and a curvature greater than 60 degrees. Additionally, those patients with an hourglass deformity or a lateral curvature seem to do better with grafting procedures. However, patients must be willing to accept higher risk of postoperative ED, along with the greater chance for penile numbness resulting from mobilization of the neurovascular bundle.

Summary

Although a multitude of articles have been written about Peyronie's, very little definitive material is available to standardize the treatment of this disease. Perhaps future studies will provide insight into appropriate patient and treatment stratification.

The current approach suggests in the acute phase patients with smaller plaques resulting in curvature less than 30 degrees may benefit from minimally invasive therapies—particularly for resolution of pain. In addition, injection therapies may offer some relief for those with early plaque formation. However, significant long-term disease regression has yet to be demonstrated for non-surgical options. Surgical approaches may provide significant improvements to appropriately selected patients. The algorithm provided in Figure 1 may serve as a useful clinical and surgical approach to the Peyronie's patient. □

References

1. Gelbard MK. Peyronie's Disease. AUA Update Series 2002; lesson 29, volume XXI.
2. Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B, Engelmann U. The prevalence of Peyronie's disease: results of a large survey. *BJU Int* 2001;88:727
3. Tefekli A, Kandirali E, Erol H, Alp T, Koksal T, Kadioglu A. Peyronie's disease in men under age 40: characteristics and outcome. *Int J Imp Res* 2001;13(1):18-23.
4. Carrieri MP, Serraino D, Palmiotto F, Nucci G, Sasso F. A case-control study on risk factors for Peyronie's disease. *J Clin Epid* 1998;51:511-515.
5. Ralph DJ, Schwartz G, Moore W, Pryor JP, Ebringer A, Bottazzo GF. The genetic and bacteriologic aspects of Peyronie's disease. *J Urol* 1997;157:291-294.
6. Newberg LM, Bias WB, Ocher MC, Walsh PC. Identification of an inherited form of Peyronie's disease with autonomic dominant inheritance and association with Dupuytren's contracture and histocompatibility B7 cross-reacting antigens. *J Urol* 1982;128:48-51.

7. Rompel R, Weidner W, Mueller-Eckhardt G. HLA association of idiopathic Peyronie's disease: an indication of autoimmune phenomena in etiopathogenesis? *Tissue Antigens* 1991;38: 104-106.
8. Nachtsheim DA, Rearden S. Peyronie's disease is associated with an HLA class II antigen HLA-DQ5, implying an autoimmune etiology. *J Urol* 1996;156:1330-1334.
9. Gholami SS, Lue TF. Peyronie's Disease. *Urol Clin North Am* 2001;28(2):377-390.
10. Devine CJ, Somers KD, Ladaga LE. Peyronie's disease: pathophysiology. *Prog Clin Bio Clin Bio Res* 1991;37:355-358.
11. Hellstrom WJ, Bivalacqua TJ. Peyronie's Disease: Etiology, Medical, and Surgical Therapy. *J Androl* 2000;21(3):347-354.
12. Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. *NEJM* 1994;331:1286-1292.
13. El-Sakka AI, Hassan MU, Nunes L, Bhatnagoor RS, Yen TS, Lue TF. Histological and ultrastructural alteration in an animal model of Peyronie's disease. *Br J Urol* 1998;81:445-452.
14. Weidner W, Scroeder-Printzen I, Weiske W, Vosshenrick R. Sexual dysfunction in Peyronie's disease: An analysis of 222 patients without previous local plaque therapy. *J Urol* 1997;157:325.
15. Lopez JA, Jarow JP. Penile vascular evaluation of men with Peyronie's disease [comments]. *J Urol* 1993:149:53-55.
16. Ralph DJ, Pryor JP. Peyronie's disease. In: Carson CC, Kirby R, Goldstein I, eds. Textbook of Erectile Dysfunction. Isis Medical Media: Boca Raton 1999:521 pp.
17. Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. *J Urol* 1990;144:1376-1380.
18. Scardino PL, Scott WW. The use of tocopherols in the treatment of Peyronie's disease. *Ann NY Acad Sci* 1949;52:390-401.
19. Ehrlich H, Bornstein P. Microtubules in transcellular movement of procollagen. *Nature* 1972;238:257-260.
20. Harris EJ, Krane S. Effects of colchicines on collagenase in culture of rheumatoid synovium. *Arthritis Rheum* 1971;14:669-684.
21. Akkus E, Carier S, Rehman J, Breza J, Kadioglu A, Lue TF. Is colchicine effective in Peyronie's disease? A pilot study. *Urology* 1994;44:291-295.
22. Safarinejad MR.Therapeutic effects of colchicine in the management of Peyronie's disease: a randomized double-blind, placebo-controlled study. *Int J Impot Res* 2004;16:238-243
23. Zarafonetis CD, Horrax TM. Treatment of Peyronie's disease with Potaba. *J Urol* 1959;81:770-772.
24. Weidner W, Hauck EW, Schnitker J. Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. *Eur Urol* 2005;47:530-535.
25. Colletta AA, Wakefield LM, Howell FV, van Roozendaal KE, Danielour D et al. Anti-oestrogen induced secretion of transforming growth factor beta from human fetal fibroblasts. *Br J Ca* 1990;62:405-409.
26. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. *J Urol* 1994;151:1522-1524.
27. Lee RC, Ping JA. Calcium antagonists retard extra cellular matrix production in connective tissue equivalent. *J Surg Res* 1990;79:40-42.
28. Steiger M, Ohig W, Ludwig G. Verapamil versus Placebo als Injektionstherapie der Induratio penis plastica: Lang-zeitergebnisse einer Doppel-blind-Studie. *Urologe A* 1999;38:S58.
29. Bennett NE, Guhring P, Mulhall JP. Intralesional verapamil prevents the progression of Peyronie's disease. *Urology* 2007;69:1181-1184.
30. Redman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urology* 1998;51:620-626.
31. Williams G, Green NA. The non-surgical treatment of Peyronie's disease. *Br J Urol* 1980;32:392-395.
32. Gelbert MK, Walsh R, Kaufmann JJ. Collagenase for Peyronie's disease experimental studies. *Urol Res* 1982;10:135-140.
33. Gelbert MK, Linder A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. *J Urol* 1985;134:280-283.
34. Gelbard MK et al. Collagenase Versus Placebo in the Treatment of Peyronie's Disease: A Double-Blind Study. *J Urol* 1992;149:56-58.
35. Jordan GH. The Use of Intralesional Clostridial Collagenase Injection Therapy for Peyronie's Disease: A Prospective, Single-Center, Non-Placebo Controlled Study. *J Sex Med* 2008;5: 180-187.
36. Duncan M, Berman B, Nseyo U. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons alpha, beta, and gamma. *Scand J Urol Nephro* 1991;25:89-94.
37. Wegner HE, Andersen R, Knispel HH, Miller K. Local interferon-alpha 2b is not an effective treatment in early-stage Peyronie's disease. *Eur Urol* 1997;32(2):190-193.
38. Judge IA, Wisniewski ZS. Intralesional interferon in the treatment of Peyronie's disease: In a pilot study. *Br J Urol* 1997;70:42.
39. Wegner HE, Andersen R, Knispel HH, Miller K. Local interferon-alpha 2b is not an effective treatment in early-stage Peyronie's disease. *Eur Urol* 1997;32(2):190-193.
40. Hellstrom WJ, Kendirci M, Matern R et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. *J Urol* 2006;176:394-398.
41. Morales A, Bruce AW. The treatment of Peyronie's Disease with parathyroid hormone. *J Urol* 1975;114:901-902.
42. Hauck E, Mueller U, Bschleipfer T, Schmelz HU, Diemer T, Weidner W. Extracorporal Shock Wave Therapy for Peyronie's Disease: Exploratory Meta-Analysis of Clinical Trials. *J Urol* 2004;171:740-745.
43. Skolarikos A, Alargof E, Rigas A, Deliveliotis Ch, Konstantinidis E. Shockwave therapy as first-line treatment for Peyronie's disease: a prospective study. *J Endourol* 2005;19:11-14.
44. Srirangam SJ, Manikandan R, Hussain J, Collins GN, O'Reilly PH. Long-term results of extracorporeal shockwave therapy for Peyronie's disease. *J Endourol* 2006;20:880-884.
45. Martin DJ, Badwan K, Parker M, Mulhall JP. Transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea. *J Urol* 2002;168:2483-2485.
46. Fitch WP 3rd, Easterling WJ, Talbert RL, Bordovsky MJ, Mosier M. Topical verapamil HCL, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease—a placebo-controlled pilot study. *J Sex Med* 2007;4:477-484.
47. Montorsi F, Guazzoni G, Bocciardi A, Barbieri L, Camp B. Transdermal electromotive multi-drug administration for Peyronie's disease: a randomized, double-blind, placebo-controlled, partial cross-over study. *J Urol* 1995;153:472-(972A).
48. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Giurioli A, Jannini EA, Vespasiani G. A prospective, randomized study using electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol* 2004;171:1605-1608.
49. Di Stasi SM, Giannantoni A, Capelli G, Jannini EA, Virgili G, Storti L, Vespasiani G. Transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *BJU Int* 2003;91:825-829.
50. Jordan GH. Peyronie's Disease. *Atlas Urol Clin North Am* 1993;1(1): 93.
51. Levine, LA. Peyronie's Disease—General review and medical therapy. 96th Annual AUA Meeting. 2001.
52. Wilson SK, Delk JR II. A new treatment for Peyronie's disease: Modeling the penis over an inflatable penile prosthesis. *J Urol* 1994;152:1121-1123.
53. Nesbit R. Congenital curvature of the phallus: Report of three cases with description of corrective operation. *J Urol* 1965;74:497-500.
54. Pryor J, Fitzpatrick J. A new approach to the correction on the penile deformity in Peyronie's disease. *J Urol* 1979;122:622-623.

55. Lemberger RJ, Bishop MC, Bates CP. Nesbit's operation for Peyronie's disease. *Br J Urol* 1984;56:721-723.
56. Yachia D. Modified corporoplasty for the treatment of penile curvature. *J Urol* 1990;143:80-82.
57. Gelbard MK. Correction of Penile curvature using tunica albuginea plication, flaps, and expansion with fascial grafts. In Ehrlich RM, Alter GJ, eds. Reconstructive and Plastic surgery of the External Genitalia. WB Saunders: Philadelphia, 1999.
58. Gholami SS, Lue TF. Correction of Penile Curvature Using The 16-Dot Plication Technique: a Review of 132 Patients. *J Urol* 2001;167:2066-2069.
59. Ralph DJ, Al-Akraa M, Pryor J. The Nesbit operation for Peyronie's disease: 16-year experience. *J Urol* 1995;154:1362-1363.
60. Licht MR, Lewis RW. Modified Nesbit procedure of the treatment of Peyronie's disease: A comparative outcome analysis. *J Urol* 1997;158:460-463.
61. Rehman J, Benet A, Minsky LS, Melman A. Results of surgical treatment for abnormal penile curvature: Peyronie's disease and congenital deviation by modified Nesbit plication. *J Urol* 1997;157:1288-1291.
62. Devine C, Horton C. Surgical treatment of peyronie's disease. *J Urol* 1974;111:44-49.
63. Austoni E, Collmbo F, Mantovani F. Chirurgia radicale e conservazione dell'erezione nella malattia di La Peyronie. *Arch Ital Urol Nefrol Androl* 1995;67:359-364.
64. Gelbard M, Hayden B. Expanding contractures of the tunical albuginea due to Peyronie's disease with temporalis fascial free grafts. *J Urol* 1991;145:772-776.
65. Egydio PH, Lucon AM, Arap S. A single relaxing incision to correct different types of penile curvature: surgical technique based on geometric principles. *BJU Int* 2004;94:1147-1157
66. Austoni E, Mnatovani F, Colombo F, Candinin L, Mastromarino G. Erectile complications after radical surgery for penile plastic induration. *Arch Ital Urol Androl* 1994;66:19.
67. Rigaud G and Berger R E. Corrective procedures for penile shortening due to Peyronie's disease. *J Urol* 1995;153:368.
68. Bystrom J, Alfthan O, Johansson B, Korlof B. Induratio penis plastica (Peyronie's disease): Results after excision and dermo-fat grafting. *Scand J Plast Reconstr Surg* 1973;7:137.
69. El-Salla AI, Rashwan HM, Lue TF. Venous patch graft for Peyronie's disease. Part II: Outcome analysis. *J Urol* 1998;160:2050-2053.
70. Kalsi J, Minhas S, Christopher N, Ralph D. The results of plaque incision and venous grafting (Lue procedure) to correct the penile deformity of Peyronie's disease. *BJU Int* 2005:95:1029-1033.
71. Benzel EC, McMillan R, Fowler MR, Landreneau MD, Kesterson L, Payne DL. Histological comparison of autologous canine fascia lata, Gore-Tex, lyophilized human fasica lata, and autogenous canine vein for vascular patch graft in a canine arteriotomy model. *Neurosurgery* 1992;3:108-113.
72. Hafez AT, Smith CR, McLorie GA, El-Ghoneimi A, Herz DB, Khoury AE. Tunica vaginalis for correcting penile cordee in a rabbit model: Is there a difference in flap vs. graft? *J Urol* 2001;166:1429-1432.
73. Kadioglu A, Sanli O, Akman T, Ersay A, Guven S, Mammadov F. Graft Materials in Peyronie's Disease Surgery: A Comprehensive Review 2008;4:581-595.
74. Breyer BN, Garcia MM, Brant WO, Bella AJ, Lue TF. Outcomes and complications of porcine small intestine submucosal graft in the surgical management of Peyronie's disease. *J Urol* 2006;175: A:999.
75. Brannigan RE, Kim ED, Oyasu R, McVary KT. Comparison of tunica albuginea substitut4es for the treatment of Peyronie's disease. *J Urol* 1998;159:1064-1068.