Peyronie's disease: update on medical management and surgical tips

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Peyronie's disease is a scarring phenomenon of the penis causing various deformities; initially pain with erection, and in most patients is associated with some element of erectile dysfunction. Studies of the natural history of the disease show that Peyronie's disease is a self-limited condition. In its stable and quiescent phase, patients have stable deformity, and in some cases that deformity then requires surgery.

For the most part, pharmacologic therapy is confined to the immature or active phase of the disease. Pharmacotherapy is aimed at trying to adjust or interfere with the scarring process, so that the resultant scar causes as little disability as possible to the patient. Most pharmacotherapy is thus useful only in the active/immature phase of disease. In the mature or quiescent phase of the disease, therapy is aimed at undoing the effects of the scarring lesion. Those therapies for the most part can be considered "scar revisions". There is no best surgical therapy, and unfortunately because the disease process generally evolves with the background of erectile dysfunction, often times with surgery there is progression of the erectile dysfunction. All patients should be counseled with regards to the option of continued watchful waiting. Patients who are operated on must be counseled with regards to realistic outcomes.

Key Words: acquired curvature, Peyronie's disease, plastic induration of penis

Introduction

Peyronie's disease is a scarring phenomenon affecting the tunica albuginea of the corpora cavernosa.[1] Scar tissue forms "plaques" that can result in pain with erection, penile curvature/deviation, penile shortening, indentations, and erectile dysfunction. It is associated with difficulty with sexual intercourse, loss of self-esteem, and depression. Peyronie's disease was probably first described in 1561 by Fallopius. However, the disease has derived its' name from Francois de la Peyronie. The disease was described by him in a manuscript in 1743. In Europe, it tends to be referred to plastic induration of the penis or induratio plastica pene. Peyronie's disease is incurable. Couples afflicted with Peyronie's disease require significant education and reassurance. Medical therapy has a place, although well performed studies proving efficacy of medical therapy for the most part have not been done. Fortunately few patients require surgery.

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Associated entities and demographics

The fibrous lesions which occur in the tunica albuginea impede expansion of the tunica albuginea causing curvature and/or indentation and/or foreshortening. These fibrous lesions are usually associated with the septal insertion usually dorsally, occasionally ventrally. Multiple lesions can occur in the same patient.

A number of entities have been implicated as being associated with Peyronie's disease. Beta blockers were felt to be causative; however, the association of beta blockers has not been proven durable. At the time beta blockers were implicated, they had just been introduced, and many of the patients treated for hypertension were on first generation beta blockers. If there is an association of beta blockers, it is probably due to the erectile dysfunction that can be caused by beta blockers. Dilantin (phenytoin) has been implicated as being associated with Peyronie's disease. During post-marketing trials of phenytoin, patients were noted to develop gingival hyperplasia, and there also were patients who developed Peyronie's disease. The two afflictions were considered possibly related; hence, phenytoin carries the warning in the Physician's Desk Reference® (PDR) that it can be associated with Peyronie's disease. The association with Paget's disease of the bone was described by Lyles[2] in a very nice study from the University of North Carolina. Subsequent studies have not been done; however, the results of that study did show an association. Diabetes mellitus has been associated with the development of Peyronie's disease. Interestingly diabetes mellitus is associated with the development of Dupuytren's disease. Whether it is the diabetes per se or again the erectile dysfunction in the case of Peyronie's disease is not clear. Dupuytren's disease is familial and is caused by an autosomal dominant gene. In patients with Peyronie's disease, coincident Dupuytren's is found in about 10%-40%. In patients with Dupuytren's, approximately 15%-30% will be found to have Peyronie's disease.[3,4] Other incidence figures vary. Jordan in 1999 reports a symptomatic incidence of 1%.[5] Lindsay in an article implicating rheumatoid arthritis and hypertension as being associated with Peyronie's disease found a prevalence of 0.4%.[6] Smith in a histologic study found asymptomatic prevalence of approximately 22%.[1] It is a disease of 45-65 with a mean age of onset of 53 years of age.[7,8] These are the years of loss of tissue elasticity, and the years of development of subtle erectile dysfunction. Whether erectile dysfunction causes Peyronie's disease, or vice versa, remains debated. I think many believe now that erectile dysfunction may be one of the causative factors leading to the development of Peyronie's disease.

Etiologic considerations and pathology

In a most commonly accepted etiology, Peyronie's disease is caused by trauma to the insertion of the septal fibers.[9-11] This trauma is then associated with inflammation, and then that inflammatory process becomes a disordered wound healing process.[12] Peyronie's disease is a self-limited condition. As the disease goes to maturity and quiescence, the patient is left with a scar that is out of proportion to any trauma that might have caused it.

The trauma to the insertion of the septal fibers causes intravasation of blood products into the traumatized area. This activates the fibrinogen cascade and mature Peyronie's plaques are found to contain fibrin deposits.[13] The midline septal insertion seems to be vulnerable with buckling. The septal fibers insert into the inner circular layer, there is no septal attachment of the inner circular layer to the outer longitudinal layer allowing for trauma to cause a delamination process.

As mentioned, Peyronie's disease is associated with Paget's disease of the bone[2] and Dupuytren's disease.[3] While certain LHRH subtypes were implicated as being related to Peyronie's disease by Leffell, however, those associations are not conclusively proven in that inadequate numbers of patients were examined.[14] Stewart proposed an association autoimmune disease,[15] however, Schiavino examined a number of autoimmune variables and found no evidence of Peyronie's disease being an autoimmune disease.[16] Diegelman has found that the plaque of Peyronie's disease is clearly associated with hyperactive wound healing.[12]

In Smith's histologic study, he found round cell infiltration in the space between the erectile tissue and the overlying tunica albuginea/developing plaque.[1] These round cells were inflammatory cells, and the notice of these cells has guided much of medical therapy sine they were noticed. Eventually this space, termed the space of Smith, becomes obliterated. Somers identified fibrin deposits in mature Peyronie's plaques and this is unusual to the scars of Peyronie's disease. The histology of the plaque is characterized by dense collagen with decreased elastin content. Plaques can undergo dystrophic calcification and in some cases cartilaginous metaplasia.[13]

If one examines the anatomy of the tunica albuginea, the tunica albuginea is bilaminar throughout most of its circumference. However, the outer longitudinal layer attenuates at roughly the 5 o'clock and 7 o'clock position, hence the ventral midline is monolaminar. The tunica albuginea is thinnest at the 3 o'clock and 9 o'clock position and thickest at the dorsal midline, and at the areas of attenuation at the 5 o'clock and 7 o'clock position.

Because the ventral tunica albuginea is monolaminar, the dorsum is felt possibly to be vulnerable to buckling trauma and this may be an explanation for the fact that most Peyronie's disease causes dorsal curvature and most Peyronie's plaques are prominently dorsal.[17]

The tunica albuginea is comprised of collagen that is brittle. The compliance of the tunica albuginea is due to the fact that collagen is arranged in helices which can straighten. Then with further distraction the collagen can slide one collagen fibril against the other. The elastin which are arranged at right angles to the collagen stretches. The elastic stretches only to a certain point, at which point the tunica becomes further noncompliant. Any further stretching occurs with displacement of the mucopolysaccharide ground substance.[18]

As mentioned, repeated mechanical stress causing microvascular trauma is felt to be associated with the development of Peyronie's disease. This causes delamination, bleeding within the tunica albuginea, and activation of the fibrinogen cascade.[13] The body floods the area with inflammatory cells which initially serve mechanical function but then secrete a number of very potent vasoactive factors.[19] In that the layers of the tunica albuginea are relatively avascular, the inflammatory reaction has been described as "trapped". Vasoactive factors such as platelet derived growth factors A&B and transfer growth factor beta 1 have been implicated. With regards the implication of transforming growth factor beta 1, this growth factor has been implicated in other soft tissue fibrosis, and is implicated in erectile dysfunction. Transforming growth factor beta 1 causes increased synthesis of fibroblasts, increased connective tissue, inhibits the activity of collagenases, and can induce its own production.[20-22]

Peyronie's disease is a disease of phases with an active or immature phase during which the patient may have painful erections, and usually notices migratory deformity. During the secondary or quiescent phase, the pain resolves, and the deformity stabilizes.[7]

Psychological aspects

The psychological aspects of Peyronie's disease are very poorly defined in the literature and much of the literature mentions the psychological aspects only in passing. Jones has described the counseling of Peyronie's patients as like unto the counseling associated with one who has suffered a death. The patient deals with many of the same mechanisms which include denial, ambivalence, anxiety, and depression. Added to this are shame, embarrassment, and self-disgust. Peyronie's patients have been described as patients with aging tissues, but a youthful libido. They are found to relate with intercourse. Peyronie's patients are not talkers, and as such they do not like to talk about their Peyronie's problem. These couples are in significant stress and many have been told that Peyronie's disease is the "end of their sex life". They admit that they are coping poorly. They do believe that "sex" is intercourse. It is imperative when initially encountering Peyronie's couples to encourage them to keep "sexual expression" alive.[23,24]

With regards to the plaques or induration, many patients are not aware of having these plaques. The fibrosis can descend along the septal fibers and the plaques can be multiple. As already mentioned, they are usually dorsal. The pain is usually only with erections, however, pain with erection and pain with intercourse should not be confused. Pain with erection inevitably resolves as the disease process enters the mature phase, however, pain with intercourse can persist. While the curvature of Peyronie's disease is usually dorsal, the curvature can be complex with significant lateral components. In most patients, some element of indentation of the corpora cavernosa can be noted.

The reported incidence of erectile dysfunction is variable. Most however would agree that a reasonable reported incidence is about 40%.[10]

Studies of Peyronie's plaques as mentioned show reduced elastin and an increase in type-3 collagen. Peyronie's disease is associated with veno-occlusive problems, Ralph feels that the cavernosal fibrosis can interfere with arterial flow. This has not been verified by other investigators. [1,13,25]

Medical/nonsurgical management

Medical management of Peyronie's disease is for the most part completely anecdotal. Agents are tried based on the intellectual aspects of their proposed mechanism of action. During the active phase, all pharmacological treatment aims to steer the process of fibrosis. Thus some agents would aim to diminish oxidative stress. Oxidative stress occurs during trauma, the free radicals are released and perpetuate further oxidative stress. Thus the number of agents is used because they purge the system of free radicals. Further healing as mentioned involves inflammation, and there appears to be some merit in addressing the entire inflammatory milieu. This should not be confused with stating that the treatment of Peyronie's disease is improved by using anti-inflammatory drugs. Most anti-inflammatory drugs address the results of the inflammatory milieu, but do nothing to diminish the inflammatory milieu. As mentioned, the phase of inflammation becomes one of

disordered wound healing governed by a number of growth factors and transforming growth factor beta 1 has been implicated. Thus drugs that purge the system of transforming growth factor beta 1 have been tried. Fibrosis involves the creation of collagen. The formation of collagen can be blocked at its inception, by either blocking the precursors to collagen or by blocking the exocytosis of collagen per se. A number of agents have been tried, vitamin E as an anti-oxidant and free radical scavenger.[26] Potaba has been proposed and is a direct blocker of fibrosis.[27] Allegra is a non-specific antihistamine and is aimed at diminishing the inflammatory milieu.[28] Colchicine[29,30] and Tamoxifen have been proposed as useful.[31,32] Carnitine which aids in blocking inflammation in blood vessels has been suggested to have efficacy.[33,34] Pentoxifylline (Trental) has been proposed.[35] This drug has the rather unique property of increasing vascularity, by diminishing the viscosity of red blood cells. Natulin was proposed and that has not been shown beneficial and has been taken off the market. There is no indication for the use of oral steroids or non-specific anti-inflammatory drugs.

The use of non-on-demand PDE5 inhibitors has been recently proposed.[36] Its use is based on the notice that in a number of situations, antifibrotic agents appear to be down-regulated. Cyclic GMP functions as an anti-fibrotic, and hence PDE5 inhibition is felt to possibly be useful in increasing the milieu of the cyclic GMP antifibrotic. Unfortunately rigorous well designed studies are lacking. As it stands now, the role of oral therapy seems to alter the progress of the disease and all oral agent use is probably limited to the acute phase of disease. Intralesional injection protocols have used steroids in the past. A WHO statement has suggested no place for the use of steroids.[37,38] Parathyroid hormone was proposed in a study by Morales.[39,40] That study did show efficacy, no further verifying studies have been done. Orgotein was proposed as an intralesional injection agent, Orgotein has been taken off of the market in all countries.[41] Verapamil, a calcium channel blocker, has been proposed as an intralesional injection agent. This agent has probably been used more than any other agents. Its use is based on the fact that fibrinectin and glycoaminoglycans are inhibited thus diminishing the production of collagen.[42,43] Interferon alpha 2 beta has also been proposed as useful, and it works by a very similar mechanism.[44] Recently clostridial Collagenase has been proposed.[45] This agent is available only in clinical trials. Collagenase being an enzyme, the method of action is different. Simply stated, the use of Collagenase suggests that it can create "chemical incisions" which can allow the plaque to expand and which can reinitiate the process of modeling. A number of topical agents have been suggested, the agent most commonly used now is topical verapamil, however, there is really no proven efficacy, single reports report anecdotal usefulness. Lithotripsy has been proposed. Its rationale for use is somewhat questionable and difficult to understand.[46,47] There are no blinded and controlled studies. There are no studies that show proven efficacy. There is a question of having ill-effects on erectile tissue, lithotripsy has been proposed as possibly useful as an adjuvant to intralesional injection therapy. A number of combined therapy protocols have been proposed.

Surgical therapy

As mentioned, future research would appear to be aimed at the topic of down regulation of "anti-fibrotics". The matrix metalloproteinase have been found to be down regulated, and appear to be selectively down regulated in Peyronie's disease.[48] Alpha 1 antitrypsin has been found to be down regulated in Peyronie's patients by Hauck.[49] However, further studies show equal down regulation in aged matched individuals. The down regulation of cyclic GMP with erectile dysfunction has already been discussed.[36]

Patients become surgical candidates when the deformity and/or the erectile dysfunction precludes intercourse. Patients must be in the stable or quiescent phase of disease and most centers would suggest at least a year from onset of symptoms. The deformity should be stable for at least 3-6 months, the patients must be pain-free (pain with erection-free). These patients benefit from detailed assessment of erectile dysfunction with stratification. It is imperative that patients be truly informed of what can be accomplished. What is accomplished is that patients can be provided a penis which is adequate for intercourse.

Generically speaking, surgical procedures can be lumped into those that shorten the long side, or those that lengthen the short side. Those that shorten the long side are either plication, tunical resection procedures, or corporoplasty procedures. There are many procedures that are described, the Peyronie's surgeon must be versed with all. Certainly plication or corporoplasty procedures have a prominent place in the surgical management of Peyronie's disease.

With regards to procedures that lengthen the short side, these are the procedures that either excise the plaque or incise the plaque and replace the corporotomy defect with graft material of some kind. By and large, excision of the plaque has been replaced by incision procedures. A number of graft materials

have been proposed. Those that have stood the test of time are dermal grafts,[50] vein grafts,[51] and some of the recently used off-the-shelf grafts. Cadaveric pericardium has been proposed as useful,[52] and the Surgisis Biodesign graft has been proposed as useful.[53]

In patients with poor erectile dysfunction and Peyronie's disease, there clearly is a place for prosthetic implantation. Wilson's[54] description of the modeling procedure has allowed patients to have their penis straightened at the time of prosthetic implantation without the need for incisions or incisions and grafting.

Summary

In summary, surgery for Peyronie's disease is palliative. It is imperative that patients have realistic expectations. It is also important that patients understand that medical therapy has not been subjected to rigorous testing, and the use of medical therapy, in large part, is anecdotal. However, the vast majority of patients with Peyronie's disease can be improved. In many, it is an improvement of their psyche by reassurance and education. However, in many surgery can restore patients to a useful sexual interaction. It must be remembered, however, that the disease is self-limited, that many of the variables that have been measured previously as indicators of pharmacologic treatment efficacy are actually part of the natural progression of the disease. The worst thing that a surgeon can do with a Peyronie's patient is rush them to the operating table in haste.

Disclosure

Dr. Gerald Jordan is an investigator and lecturer for Auxilium Pharmaceuticals, a board member of Engineers & Doctors and director, medical development of PNN. He is a speaker for American Medical Systems and a consultant for Coloplast. □

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