CASE REPORT

Peyronie's disease: A "triple oxygenant therapy"

Francesco Ciociola [1], Giovanni Maria Colpi [2]

[1] Specialista in Endocrinologia e Malattie del Ricambio - Consulente Andrologo - U.O.C. Urologia 2 - Andrologia e Riproduzione Assistita, Azienda Ospedaliera San Paolo - Polo Universitario, Milano, Italy;
[2] Specialista in Andrologia, Urologia ed Endocrinologia - Direttore U.O.C. Urologia 2 - Andrologia e Riproduzione Assistita, Azienda Ospedaliera San Paolo - Polo Universitario, Milano, Italy.

Summary

Objectives: To evaluate the effects of upregulators of nitric oxide in one patient with Peyronie's disease, after non significant improvement following intracavernosal verapamil.
Methods: A 20-years-old Caucasian male presented with penile induration in flaccid state, persistent during erection and associated with mild pain at third middle of penis. After treatment with intracavernosal verapamil for 4 months with relief of penile discomfort, followed by counseling on the use of penile extender for at least 6 hours per day, he was prescribed pentoxifylline associated with tadalafil plus levo-arginine, propionil-carnitine and Vitamin B3.
Results: After almost 2 years, the septal thickness was reduced at ultrasound evaluation after this "triple oxygenant therapy".
Conclusion: NO-iNOS biology in Peyronie patients is the very protagonist in modulating penile fibrosis through up-regulation of NO-cGMP pathway that influences penile health by preventing and reversing fibrosis in the tunical albuginea.

KEY WORDS: *Peyronie's disease; Pentoxifylline; Penile fibrosis; Phosphodiesterase inhibitors; Tadalafil; L-arginine.*

Submitted 31 July 2012; Accepted 31 December 2012

No conflict of interest declared

INTRODUCTION

Peyronie's disease (PD) is characterized by the development of a fibrotic process involving the tunica albuginea. Information on the prevalence is not homogeneous but generally it is assumed that approximately 5% of men aged 50 years or older will experience the disease (1). The penile fibrosis may begin with a variety of penile deformities including curvature, notching, palpable nodule or plaques, hourglass narrowing, penile shortening (with or without curvature), difficulty with coitus and erectile dysfunction. The average age of onset is 53 years, varying between 40 and 60 years of age, but the disease is known to occur in patients as young as 18 years of age (3). *Mulhall* reported that untreated PD resolves in only 12% of men, with 40-48% of men demonstrating worsening of curvature at 12 months, and stable curvature in the remaining men (4). Despite a general perception that the condition is benign, PD is progressive and can have significant emotional and psychological consequences in men with this condition. The exact etiology of PD remains unknown and is likely multifactorial (1). PD is the result of a complex interplay between genetic predisposition, trauma and trapped inflammation. The presence of Dupuytren's contractures among some men with PD suggests that a genetic predisposition to scarring and fibrosis may be associated with tunica albuginea fibrosis and scarring.
The concept introduced by *Horton* and *Devine* that trauma to the penis leads to PD continues to be accepted two decades after its introduction (5), but as potential contributors to the pathogenesis of plaque, we can also include failure of fibrin degradation, altered collagen deposition in the tunica albuginea with a shift in the type of collagen released from predominant type I to type III, resulting in extracellular matrix scarring, production of free radicals (peroxynitrite) in cavernosal tissue of men with PD (6).
Bivalacqua et al. have demonstrated increased levels of iNOS protein and decreased levels of eNOS protein in

the cavernosal tissue of men with PD 7. The production of iNOS is stimulated by cytokines (IL-1, TNF-α), interferon and NF-kB; at supraphysiological levels, NO resulting from iNOS upregulation in smooth muscle cells and macrophages starts to play a role as an oxidant generator (7). However, the role of iNOS in wound healing is confusing because under certain circumstances it promotes wound healing while under others it maybe fibrogenic and destructive (8).
Furthermore, Vernet et al have explored the impact of NO on fibroblast differentiation in the rat model of PD: chemical inhibition of iNOS resulted in an increase in myofibroblast number, suggesting that iNOS may play some role in limiting the myofibroblast population in an effort to reduce tunical scarring and contraction (9).

Case report

A 20-years-old Caucasian male reported the evidence of penile induration in flaccid state, persistent during erection and associated with mild pain at third middle of penis. This mass appeared only 2-3 weeks before the consultation, but then it remained stable in size and discomfort. At the beginning, he ruled out any penile curvature or shortening during erection and his sexual activity was normal with regular vaginal intercourses twice a week. The patient denied any traumatic injury or acute pain during intercourse or masturbation before the development of this condition.
His general health was excellent; he didn't report use of alcool, tobacco, illegal drugs or other medications. He ruled out family history of this condition or other fibrotic disease such as scleroderma, Dupuytren's contractures or Lederhose's disease (aponeurotic plantar fibrosis). On physical examination, the patient presented only keloid fibrotic scar for previous abdominal surgery for appendicitis; his hands and feet were free of fibromatosis and contractures, his left testis was normal, but right testis was reported into scrotum at the age of 2 years. The blood examinations were normal but mild hyperuricemia, so we performed diet therapy and follow-up.
After 1 month, he started with topical verapamil hydrochloride and iontophoresis applied twice a week over the entire shaft of the penis without any significant improvement of penile plaque or pain. At the end of this period, he noted penile curvature with hourglass deformity and shortening of the penis during erection without erectile dysfunction. Then, patient was elegible to intracavernosal infusion with verapamil 5 mg dissolved in phleboclysis 100 cc saline solution for 8 weeks (9) with relief of penile discomfort, followed by counseling on the use of penile extender for at least 6 hours per day (10).
His penis retained a hard palpable septal plaque at midshaft by physical examination and a fibrotic defect of 2.3 x 13.6 mm (thickness x length) was revealed by ultrasound evaluation after 10 mcg of PGE1) (Figure 1).

Treatment

After informed consent, the patient was prescribed Pentoxifylline 400 mg (*Trental R, Sanofi-Aventis Spa, Milano*) ter in die for 2 years associated with tadalafil 5 mg (*Cialis R, Eli Lilly Italia Spa, Sesto Fiorentino*) three time a week plus levo-arginine 2500 mg daily, propionil-carnitine 250 mg daily and Vitamin B3 20 mg daily (*Ezerex R, Sigma Tau Spa, Roma*). Physical examination and blood pressure measurements were planned.at regular intervals.
After 1 year, the penile plaque was of 1.9 x 12.4 mm (thickness x length) and resulted hypoechogenic at ultrasound examination (Figure 2) and soft at physical evaluation. This clinic evidence confirmed the favourable evolution of the fibrotic disease. Moreover, using penile extender for at least 6 hours daily for 1 year, the lenght of stretched penis improved from 11.5 cm at the onset of the disease to the final 14 cm, with changing of penile girth at midshaft from 11.5 cm to 12.5 cm.
The evolution was noteworthy and confirmed at almost 2 years after the beginning of treatment with a septal thickness of 1.6 x 7 mm (Figure 3) by ultrasound evaluation, but without further changes of penile length and girth.

Figure 1.

Ultrasound scan image of penis after 10 mcg of PGE1: fibrotic defect of 2,3 x 13,6 mm (thickness x lenght) before treatment.

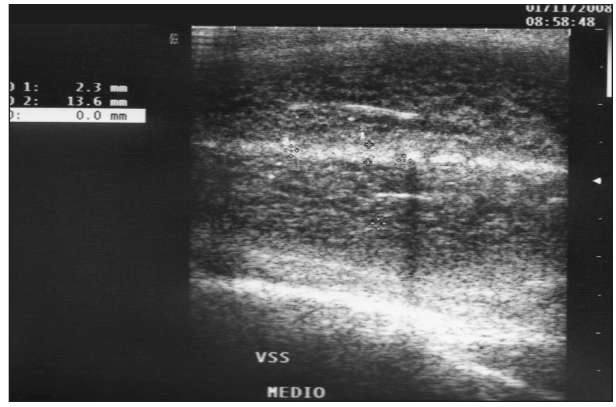


Figure 2.

Ultrasound scan image of penis: after 1 year of therapy: the penile plaque resulted of 1,9 x 12,4 mm (thickness x lenght).

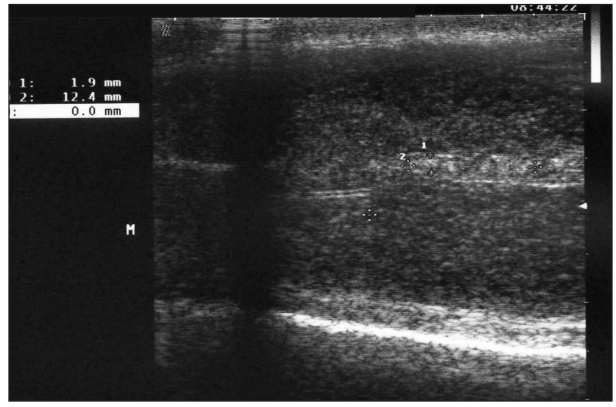
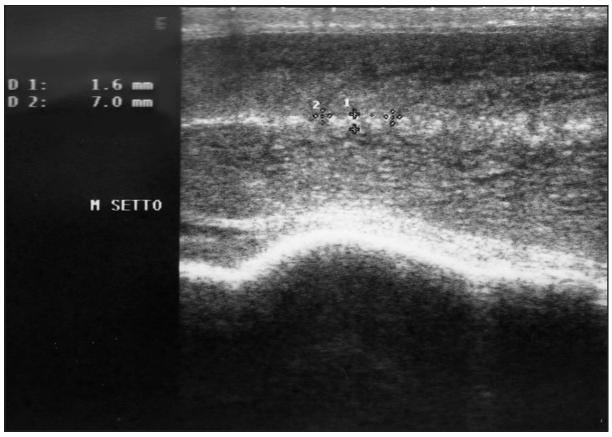


Figure 3.

Septal penile fibrosis by ultrasound scan image: almost 2 years after beginning therapy, the septal thickness resulted of 1,6 x 7 mm.



Discussion

Current papers about the origin of Peyronie's disease emphasize that collagen deposition and fibrosis of the tunica albuginea and adjacent corpus cavernosum are the result of an inflammatory process following vascular trauma. In fact, after infiltration and activation of polymorphonuclear leukocytes and macrophages, the process of wound healing is followed by a stage of fibroplasia (fibrosis) characterized by fibroblast migration and proliferation, and extracellular matrix deposition (11). A large number of growth factors and fibrogenic cytokines, such as platelet derived growth factor (PDGF), fibroblast growth factor (FGF), TGF-β, interleukin-1 (IL-1), and tumor necrosis factor (TNF-α) mediate migration of fibroblasts and their proliferation. As the repair process progresses, the number of proliferating fibroblasts and endothelial cells decreases and the fibroblasts begin to deposit collagen and other components of extracellular matrix. PDGF, FGF and IL-1 stimulate this collagen synthesis, and TGF-β is thought to play an important role in chronic inflammatory fibrosis disorders (12).

NO isoforms, particularly iNOS, have been revealed to modulate the onset and the progression of fibroblastic or wound healing process (13). In fact monocytes, macrophages and fibroblasts have been shown to synthesize NO through an NF-kB activated iNOS-dependent mechanism after injury (14). However, there is a conflicting evidence to show that NO production via overexpression of iNOS and consequent peroxynitrite loading could be an important mediator of the resolution/suppression of collagen deposition or a stimulator of collagen synthesis in injured organ (15).

Like to what has been observed in other tissues, such as heart, liver and kidney, when fibrosis develops after these tissues have been exposed to both long-term and continuous inhibition of total nitric oxide production (16), *Ferrini* (17) proposed that nitric oxide derived from iNOS activation was able to bind ROS, the profibrotic compounds produced by oxidative stress, producing peroxynitrite. This is scavenged by inducing the nitrotyrosinilation of proteins: so, peroxynitrite acts as an apoptotic but presumably non-fibrotic compound (17). Ferrini showed that in human PD plaque, as compared with normal tunica, iNOS mRNA and protein were both induced. From cell culture experiments based on incubation of fibroblast cultures from the human PD plaque and the normal tunica albuginea with iNOS inhibitor and cGMP and nitric oxide donors, the myofibroblasts resulted differentiated from normal tunica albuginea fibroblasts and increased during plaque formation. Myofibroblasts are key cells during wound healing, which, at the completion of this process, are normally eliminated by apoptosis; when they persist, this persistence leads to scar formation (18). Infact, *Vernet et al.* have explored the impact of NO on fibroblast differentiation in the rat model of PD: chemical inhibition of iNOS resulted in an increase in myofibroblast number, suggesting that iNOS may play some role in limiting the myofibroblast population in an effort to reduce tunical scarring and contraction (19).

Intriguingly, the sustained pharmacological increase of cGMP and/or nitric oxide by long-term continuous administration of drugs such as the PDE inhibitors and/or nitric oxide generators should reduce the fibrotic plaque in the TGF-β1 rat model of PD (20).

NO, as well as its product cyclic-guanosine monophosphate (cGMP), also inhibits collagen synthesis directly as demonstrated in fibroblast cultures from the normal human tunica (21). However, the role of NO in inflammation seems to be more complex, also involving beneficial effects exerted through the interference with the proinflammatory function of macrophages and lymphocytes. Contradictory effects of cyclic-adenosine monophosphate (cAMP) on macrophages NO release might partly be explained by dual, dose-dependent role of intracellular cAMP rise in iNOS induction in these cells, with higher cAMP concentrations exerting inhibitory effect (22).

On the other hands, it has been demonstrated that the enhancement of iNOS-mediated NO synthesis in these cells by cAMP-increasing PDE inhibitors. Moreover, cell-sensible iNOS modulation highlights a possible role of cGMP levels in vascular smooth muscle, in which both cGMP and cAMP regulate iNOS activation in similar manner (23). The therapeutic effects on the endothelial and cavernosal smooth muscle in the penis after long-term continuous PDE-5 inhibitor therapy involves specific molecular mechanism. Emerging evidences in this field of study underline non-erectogenic beneficial uses of PDE5-inhibitors (24), e.g. by counteracting the penile fibrotic process in a rat model of Peyronie's disease (21). Therefore, there is a possibility that some PDE inhibition-unrelated features of certain drugs or drug families might contribute to their effect on iNOS-mediated NO synthesis (23); this indeed could be the case with methylxanthines and their derivatives, the antioxidant activity of which might be partly responsible for their blocking of redox-sensitive activation of iNOS transcription factor NF-kB (25).

Methylxanthine derivative pentoxifylline is a non specific cAMP-PDE inhibitor used for a wide variety of inflammatory and fibrotic conditions. Pentoxifylline downregulates TGFβ, reduces the production of TNF, inhibits the

action of platelet-activating factor on neutrophils, and suppresses the production of platelet-activating factor.
Recently, pretreatment with pentoxifylline attenuates both collagen fiber deposition and elastogenesis in tunica albuginea-derived fibroblasts exposed to TGF-β1 (26).
Clinically, *Brant* (27), after using pentoxifylline 400 mg three times a day for 2 years demonstrated improvement of penile curvature and ultrasonographic disappearance of lesion. Furthermore, an antifibrotic regimen consisting of upregulators of NO production (pentoxifylline and sildenafil), demonstrated amelioration of the corporal fibrosis associated with recalcitrant priapism (28).
In patients with early chronic Peyronie's disease, *Safarinejad* (29) showed that almost a third of men assessed had an improvement in their curvature and about half had their deformity stabilized.
Carnitine is a naturally occurring metabolic intermediate. Propionil-L-carnitine acts as superoxide scavenger and it is protective against peroxidative damage to arterial endothelium membranes. Recent data suggest that propionil-L-carnitine and verapamil are effective in terms of plaque size reduction, pain, and penile curvature (30).
Vitamin B3 or nicotin acid, acts as vasorelaxant effect to improve peripheral arterial circulation and penile response to NO. However, Vitamin B3 is precursor of NADP (nicotine adenine dinucleotide phosphate), that is a pivotal enzymatic co-factor in redox signaling.
To date, the exact pathogenesis of PD is unknown and this case report did not reveal any potential trigger factor. The correct clinical and ultrasound recognition of the active disease may influence the treatment that should be tailore on the individual patient.
Certainly, the first 6-8 months are the most critical for the therapeutic success which remains unpredictable for both the andrologist and the patient. In our case,it is not possible to exclude a spontaneous healing of the septal fibrosis, but the young age of the patient required a careful reassessment of alternative treatment. The favourable clinical and ultrasound outcome after our protocol can not be explained as stochastic and it challenges to consider this therapeutic option.

Conclusion

This case report demonstrates that NO-iNOS biology is preeminent in Peyronie patients by modulating penile fibrosis. It stresses that up-regulation of NO-cGMP pathway can influence penile health by preventing and reversing fibrosis in the tunical albuginea.
This is the first evidence that long-term therapy with tadalafil plus pentoxifylline and L-arginine with other cofactors may modify either gene expression or protein synthesis/degradation by cyclic nucleotide ehancement.
The beneficial "*reconstitution*" of tunical/cavernosal integrity remains the "*gold standard*" for Peyronie's disease but the best practice has still to be assessed. Early identification, and assessment of patient's expectations though discussion of non-surgical treatment options aimed to stabilization of the disease are crucial. In our experience, penile length and girth gain by traction device that helps to enforce the pharmacological effects of drugs.
The clinical results so far obtained are very encouraging and should stimulate further interest in studying the potential use of PDE5 inhibitors in association with other drugs as penile antifibrotic agents. This report promotes a multi-modal approach for non-surgical therapy of Peyronie's disease aimed to sustain the blockage of the TGF-β signaling pathway.

Acknowledgements

All authors contributed to bibliographic research, critical evaluation of the articles included in the manuscript and writing of the manuscript. All authors read and approved the final manuscript. The authors declare that they have no competing interests.This study was not supported by any grant.

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Correspondence

Francesco Ciociola, MD (Corresponding Author)
Specialista in Endocrinologia e Malattie del Ricambio
Consulente Andrologo
U.O.C. Urologia 2 - Andrologia e Riproduzione Assistita
Azienda Ospedaliera San Paolo - Polo Universitario
Via Antonio di Rudinì, 8 - 20142 Milano, Italy
ciociolafrancesco@libero.it

Giovanni Maria Colpi, MD
Specialista in Andrologia, Urologia ed Endocrinologia
Direttore U.O.C. Urologia 2 - Andrologia e Riproduzione Assistita
Azienda Ospedaliera San Paolo - Polo Universitario
Via Antonio di Rudinì, 8 - 20142 Milano, Italy
gmcolpi@yahoo.com