Arab Journal of Urology (2013) **11**, 294–298

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com

REVIEW

Treatments for fibrosis of the corpora cavernosa

Paulo H. Egydio [a,*,1], **Franklin E. Kuehhas** [b,1]

[a] *Center for Peyronie's Disease Reconstruction, São Paulo, Brazil*
[b] *Medical University of Vienna, Department of Urology, Vienna, Austria*

Received 14 April 2013, Received in revised form 28 May 2013, Accepted 30 May 2013
Available online 9 July 2013

KEYWORDS

Penile fibrosis;
Corporal fibrosis;
Therapy;
Surgery;
Erectile dysfunction

ABBREVIATIONS

PD, Peyronie's disease;
ED, erectile dysfunction;
PGE1, prostaglandin E1;
ICI, intracavernous injection;
PDE5I, phosphodiesterase 5 inhibitors

Abstract ***Introduction:*** Corporal fibrosis usually occurs after explantation of an infected penile prosthesis, severe penile trauma, refractory low-flow priapism, Peyronie's disease, or the chronic intracavernous injection of vasoactive drugs.

Methods: We analysed current treatmentss for penile fibrosis. We searched PubMed using the keywords 'penile corporal fibrosis', 'treatment' and 'penile fibrosis', resulting in 63 matches, of which 19 articles met the inclusion criteria.

Results and conclusions: This review covers conservative medical therapy for corporal fibrosis and surgical therapeutic methods. The roles of phosphodiesterase- 5 inhibitors and pentoxifylline are analysed. Surgical therapy includes implantation of a penile prosthesis and corporal reconstruction, and these are reviewed. Corporal fibrosis is a major problem for patients, and is associated with severe erectile dysfunction. Conservative treatment options can be applicable in the early phase, but simultaneous corporal reconstruction procedures with concomitant implantation of a penile prosthesis should be attempted in severe cases of corporal fibrosis.
© 2013 Production and hosting by Elsevier B.V. on behalf of Arab Association of Urology.

Introduction

Penile fibrosis was assumed to be rare and limited to the formation of plaques of the tunica albuginea in patients with Peyronie's disease (PD) [1]. However, it has recently become evident that fibrosis of the corpora cavernosa and the media of the penile arteries, involving the loss of smooth muscle cells, is a highly prevalent process in most cases of vasculogenic erectile dysfunction (ED) [2]. Corporal fibrosis usually occurs after explanta-

* Corresponding author. Address: Center for Peyronie's Disease Reconstruction, Rua Joaquim Floriano 533 Cj 902, São Paulo 04534–011, Brazil. Tel.: +55 11 9194 9090; fax: +55 11 3077 3644.
E-mail address: drpaulo@drpaulo.com.br (P.H. Egydio).
[1] These authors contributed equally to this work.
Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

2090-598X © 2013 Production and hosting by Elsevier B.V. on behalf of Arab Association of Urology.
http://dx.doi.org/10.1016/j.aju.2013.05.004

tion of an infected penile prosthesis [3], severe penile trauma [4], refractory low-flow priapism [5], PD [6], or the use of chronic intracavernous injection (ICI) of vasoactive drugs [7,8]. Chew et al. [9] conducted a study on 300 consecutive clinical cases who were long-term users of prostaglandin E1 (PGE1), to ascertain the association of ICI therapy with penile fibrosis. The study results showed that 23.3% of patients developed penile fibrosis (their mean age was 62.2 years, with a mean of 5.2 times/month for the self-administered injection of PGE1, over a mean period of 29.2 months) suggesting a strong association of ICI therapy with penile fibrosis.

Another milder but progressive form of penile fibrosis that also involves penile blood vessels can develop in chronic smokers, hypertensive patients, alcoholics, elderly men, diabetics and after radical prostatectomy, presenting primarily with ED [1]. El-Sakka et al. [10] suggested a probable mechanism for the development of penile fibrosis with advancing age. Atherosclerotic processes affect the blood supply to penile tissues and that decreases oxygen tension in the smooth muscle cells, leading to regression and lack of elasticity. Prolonged ischaemic changes induced by atherosclerosis can lead to the permanent replacement of smooth muscle cells by fibrotic tissue. As most cases are reported in elderly men, a decrease in the secretion of testosterone is also a possible reason for the fibrotic changes.

The primary pathophysiological event in the development of penile fibrosis is over-expression of plasminogen activator inhibitor 1, TGF β1, and reactive oxygen species that lead to the increased activity of myofibroblasts and the elevated production, deposition and accumulation of collagen [11].

Phosphodiesterase 5 inhibitors (PDE5i) as anti-fibrotic agents

Penile fibrosis leads to significant ED in chronic and severe cases; most current treatments focus on the management of ED instead of promoting the anti-fibrotic mechanisms [11]. Treatments that focus on manipulating the activity of myofibroblasts can be effective in managing this issue in cases of mild fibrosis.

Research on animal models suggests that the continuous and long-term administration of PDE5i is not only safe but also has anti-fibrotic properties that might help to relieve fibrotic plaques in localised as well as widespread fibrosis in penile tissue. Gonzalez-Cadavid et al. [11] suggested that in localised and mild penile fibrosis in PD, the administration of PDE5i might not be the first-line therapy, due to a risk of progression of the plaque and calcification of the lesion. However, if PDE5i are co-administered with agents to break down collagen molecules in the plaque, the efficacy of the overall therapy can be increased.

El-Sakka et al. [10] suggested that the loss of smooth muscle cells and changes in the nervous and arterial supply to penile tissue is also an important cause of penile fibrosis in elderly men, and treatments should be aimed at the up-regulation of the nitric oxide/cGMP pathway in the corporal tissue. This can be achieved by the long-term administration of PDE5i.

Ferrini et al. [12] also suggested that PDE5i and the up-regulation of inducible nitric oxide synthase can be used as an active strategy to alleviate the fibrotic plaques in penile tissues. Studies on ageing rats by Ferrini et al. suggested that administering sildenafil leads to a significant increase in the ratio of smooth muscle cells to collagen, and the correction of age-related vasculogenic ED and corporal fibrosis. In another model, Ferrini et al. [12] gave vardenafil to rats with well-developed penile fibrosis. Administration of vardenafil in the drinking water for 41 days reportedly decreased the collagen in corporal tissue, with a substantial reduction of myofibroblasts and TGF β1-positive cells. According to available study data the beneficial effect of PDE5i on penile fibrosis seems to be validated. The administration of PDE5i can increase the concentration of cGMP, and in turn stimulates NO levels that are responsible for the anti-fibrotic activity associated with sildenafil, vardenafil, and long-acting once-daily tadalafil [2,13,14].

In an interesting prospective randomised study, Zahran et al. [15] analysed the role of the anti-fibrotic characteristics of pentoxifylline amongst 40 patients with prolonged ischaemic priapism. Patients were randomly divided into two groups receiving either pentoxifylline or not, from the second day after surgery for 3 months. The follow-up was 18 months. However, the authors showed no significant effect of pentoxifylline on the recovery of erectile function after a T-shunt procedure.

Penile prosthesis implantation

With extensive corporal fibrosis, a penile implant is the only viable option to alleviate sexual dysfunction [16]. In cases of scarred penile corporal bodies, the surgery becomes challenging even for experienced surgeons, as it can be extremely difficult or indeed impossible to dilate the corpora [3,17,18]. Long-standing or generalised penile fibrosis is an independent risk factor for a regression in the size of the penis that can decrease the size on erection by up to 6 cm [19]. Loss of penile length and penile girth can be solved by extensive penile graft surgery [20]. Many surgical approaches have been suggested to facilitate the implantation of a prosthesis in cases of corporal fibrosis. Traditionally, large corporotomy incisions are created to resect the scar tissue, and grafts are used to cover the corporal defects [7]. However, there is no consensus on the optimal technique for handling cases of severe corporal fibrosis [21]. For example, Dhabuwala et al. [22] described an approach involving multiple incisions and minimal scar tissue excision. These authors reported an intra- and postoperative complication rate of 2.9%. An alternative approach was described by Montague and

Angermeier [23] that involved the use of a corporeal excavation technique. After a long corporotomy incision was created, Metzenbaum scissors were used to establish a plane of dissection between the under-surface of the tunica and the fibrotic area, followed by excision of the fibrotic core. Another interesting approach was described by Shaeer et al. [24], who proposed a transcorporeal resection using optical corporotomy to excavate the fibrotic tissue under direct vision (penoscopy). A modification of the technique involves the use of ultrasonography (with a linear 7.5 MHz probe) to monitor and guide penoscopic excavation [25].

The loss of penile length is a severe problem for patients. Wilson et al. [19] reported on their experience of using larger penile implants in cases of corporal fibrosis in 37 patients. The patients were to inflate their devices for 3 h daily. These patients were poor candidates for the use of cavernotomes and smaller cylinders, due to widespread fibrosis as a result of infection of previous implants or prolonged priapism. After using inflation exercises for several months, the corporal length of the cavity increased by 2.2 cm, and that allowed surgeons to place a wider and larger implant for better functioning and patient satisfaction. The conclusion of the study was that if inflation is used regularly for 8–12 months, standard implants can be used after a period of a few weeks to months [19].

Penile lengthening techniques

Avoiding penile shortening is a crucial factor for patient satisfaction, and this has been validated in several reports. Knoll et al. [26] proposed that using a penile prosthesis in patients with extensive fibrosis is ineffective in treating ED completely, because of insufficient penile length. All these patients can benefit from a combined surgical approach that involves a modified suprapubic V-Y advancement flap along with de-bulking of the lower abdominal tissue, in addition to insertion of a penile prosthesis. Knoll et al. used this surgical approach in 11 patients, and reported an increase in penile size of 3.5–6.5 cm. At the 1-year follow-up all prostheses were fully functional and there was no sign of infection.

Many patients with corporal fibrosis also have a webbed penoscrotal union, caused by multiple operations and penile shrinkage [21]. Therefore, the cosmetic appearance can be improved by a scrotoplasty, by closing the transverse incision vertically. Sometimes a partial scar excision can also improve the final outcome.

Akin-Olugbade et al. [27] reported that the satisfaction levels of patients with PD who have a penile prosthesis implanted are lower than those of the general population with such an implant. The underlying reason is penile shortening. A 60° penile curvature before the implantation of a penile prosthesis means that the concave tunica albuginea side is 2.5–3 cm shorter than the convex side [28]. Levine et al. [6] showed that almost 60% of patients with PD felt that they had lost penile length before surgery due to the underlying disease, and up to 54% reported that they had lost further length after a prosthesis was implanted. Wang et al. [29] reported that implanting a penile prosthesis is associated with a reduction in postoperative penile length, the average loss being reported as 0.74 cm.

Corporal reconstruction

Corporal reconstruction is ideal for severe fibrosis of the corpora cavernosa that results in loss of penile length and girth [30]. The efficacy of penile implant surgery is limited by the shortness of the fibrotic corporal cavity, that increases the risk of infection, herniation and separation [16], ultimately leading to even more fibrosis. Moreover, the smaller penis hinders the resumption of sexual activity, and the efficacy of the surgical procedure is greatly limited by the smaller implant size. Therefore, simultaneous corporal reconstruction and implantation of a penile prosthesis in patients with ED and severe fibrosis of the corpora cavernosa should be attempted, to restore a functional penis.

Implantation of a penile prosthesis, with concomitant reconstruction of the corpora consisting of penile lengthening and girth restoration based on longitudinal and circular tunica albuginea incisions [31] according to geometrical principles, is a safe, valid and reliable technique in patients with PD who have severe ED and penile shortening. We showed that length and girth restoration is a crucial factor for patient satisfaction [20]. Our treatment approach of circular and longitudinal tunica albuginea incisions, and restoration of penile length, resulted in a mean (SD, range) functional penile length gain of 3.6 (0.7, 2–5) cm. The rate of patient satisfaction with the penile length gain was 95%. However, it is very important to avoid creating false expectations in patients about the recovery of the original size of the penis, as the maximum recoverable size of the penis is based on the length and elasticity of the neurovascular bundle [32]. Patients must be informed that PD might have caused structural alterations that shorten the neurovascular bundle.

Sansalone et al. [17] published their data on total corporal reconstruction with concomitant implantation of a penile prosthesis in 18 patients. They showed that although implanting a penile prosthesis into fibrotic corpora is a challenging procedure, it yields satisfactory results in expert hands. Furthermore, they concluded that patients need to be warned that the complication rate in the presence of severe corporal fibrosis is significantly higher than unaffected cases, and that smaller cylinders might be required due to the contraction of the tunica albuginea [17].

In cases of corporal reconstruction, grafting has become very popular after excision of the fibrotic spongy tissue, when the retracted tunica albuginea does not

allow closure of the corporal bodies. Grafts are necessary to avoid aneurysmal dilatation of the cylinders, erosion, migration, infection and mechanical failure of the device [21,33,34].

The most common synthetic grafts are Goretex™ and Dacron™, while the most common autologous graft materials in prosthetic surgery are the saphenous vein, dermis, buccal mucosa, rectus fascia and fascia lata. Bovine and cadaveric pericardium, porcine small intestine submucosa and cadaveric fascia lata are the main extracellular matrix grafts [17]. Each graft has advantages and disadvantages in terms of availability, antigenicity and cost-effectiveness. The main disadvantage of synthetic grafts is their immunogenicity, which translates into a significantly greater infection rate of the penile prosthesis. Problems with autologous materials are related to donor size, morbidity, limited availability and increased operative time [35].

Conclusion

Corporal fibrosis is a major problem for patients, and is associated with severe ED. Conservative treatment options can be applicable in the early phase, but simultaneous corporal reconstruction procedures with concomitant penile prosthesis implantation should be attempted in severe cases of corporal fibrosis. These procedures help to achieve the desired results, and with a better patient satisfaction profile. In every case we recommend that the different treatment options available are discussed in detail with patients, and the proper counselling of the patient about the potentially greater risks is mandatory.

Conflict of interest

None.

Funding

None.

References

[1] Gonzalez-Cadavid NF. Mechanisms of penile fibrosis. *J Sex Med* 2009;**6**(Suppl. 3):353–62.
[2] Iacono F, Giannella R, Somma P, Manno G, Fusco F, Mirone V. Histological alterations in cavernous tissue after radical prostatectomy. *J Urol* 2005;**173**:1673–6.
[3] Wilson SK. Reimplantation of inflatable penile prosthesis into scarred corporeal bodies. *Int J Impot Res* 2003;**15**(Suppl.):S125–8.
[4] Orvis BR, McAninch JW. Penile rupture. *Urol Clin North Am* 1989;**16**:369–75.
[5] Stember DS, Mulhall JP. Ischemic priapism and implant surgery with sharp corporal fibrosis excision. *J Sex Med* 2010;**7**:1987–90.
[6] Levine LA, Benson J, Hoover C. Inflatable penile prosthesis placement in men with Peyronie's disease and drug-resistant erectile dysfunction: a single-center study. *J Sex Med* 2010;**7**:3775–83.
[7] Henry GD, Laborde E. A review of surgical techniques for impending distal erosion and intraoperative penile implant complications: part 2 of a three-part review series on penile prosthetic surgery. *J Sex Med* 2012;**9**:927–36.
[8] Larsen EH, Gasser TC, Bruskewitz RC. Fibrosis of corpus cavernosum after intracavernous injection of phentolamine/papaverine. *J Urol* 1987;**137**:292–3.
[9] Chew KK, Stuckey BG, Earle CM, Dhaliwal SS, Keogh EJ. Penile fibrosis in intracavernosal prostaglandin E1 injection therapy for erectile dysfunction. *Int J Impot Res* 1997;**9**:225–9.
[10] El-Sakka AI, Yassin AA. Amelioration of penile fibrosis: myth or reality. *J Androl* 2010;**31**:324–35.
[11] Gonzalez-Cadavid NF, Rajfer J. Treatment of Peyronie's disease with PDE5 inhibitors: an antifibrotic strategy. *Nat Rev Urol* 2010;**7**:215–21.
[12] Ferrini MG, Kovanecz I, Sanchez S, Vernet D, Davila HH, Rajfer J, et al. Long-term continuous treatment with sildenafil ameliorates aging-related erectile dysfunction and the underlying corporal fibrosis in the rat. *Biol Reprod* 2007;**76**:915–23.
[13] Jeremy JY, Ballard SA, Naylor AM, Miller MA, Angelini GD. Effects of sildenafil, a type-5 cGMP phosphodiesterase inhibitor, and papaverine on cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosum in vitro. *Br J Urol* 1997;**79**:958–63.
[14] Levy I, Horvath A, Azevedo M, de Alexandre RB, Stratakis CA. Phosphodiesterase function and endocrine cells: links to human disease and roles in tumor development and treatment. *Curr Opin Pharmacol* 2011;**11**:689–97.
[15] Zahran AR, Daiem HA, Youssif M. Does pentoxifylline enhance the recovery of erectile function after a T-shunt procedure for prolonged ischaemic priapism? A prospective randomised controlled trial. *Arab J Urol* 2012;**10**:425–8.
[16] Tran VQ, Lesser TF, Kim DH, Aboseif SR. Penile corporeal reconstruction during difficult placement of a penile prosthesis. *Adv Urol* 2008;370947.
[17] Sansalone S, Garaffa G, Djinovic R, Antonini G, Vespasiani G, Ieria FP, et al. Simultaneous total corporal reconstruction and implantation of a penile prosthesis in patients with erectile dysfunction and severe fibrosis of the corpora cavernosa. *J Sex Med* 2012;**9**:1937–44.
[18] Hellstrom WJ, Montague DK, Moncada I, Carson C, Minhas S, Faria G, et al. Implants, mechanical devices, and vascular surgery for erectile dysfunction. *J Sex Med* 2010;**7**:501–23.
[19] Wilson SK, Delk JR, Mulcahy JJ, Cleves M, Salem EA. Upsizing of inflatable penile implant cylinders in patients with corporal fibrosis. *J Sex Med* 2006;**3**:736–42.
[20] Egydio PH, Kuehhas FE, Sansalone S. Penile length and girth restoration in severe Peyronie's disease using circular and longitudinal grafting. *BJU Int* 2013;**111**:E213–9.
[21] Martinez-Salamanca JI, Mueller A, Moncada I, Carballido J, Mulhall JP. Penile prosthesis surgery in patients with corporal fibrosis: a state of the art review. *J Sex Med* 2011;**8**:1880–9.
[22] George VK, Shah GS, Mills R, Dhabuwala CB. The management of extensive penile fibrosis: a new technique of 'minimal scar-tissue excision'. *Br J Urol* 1996;**77**:282–4.
[23] Montague DK, Angermeier KW. Corporeal excavation: new technique for penile prosthesis implantation in men with severe corporeal fibrosis. *Urology* 2006;**67**:1072–5.
[24] Shaeer O, Shaeer A. Corporoscopic excavation of the fibrosed corpora cavernosa for penile prosthesis implantation: optical corporotomy and trans-corporeal resection, Shaeer's technique. *J Sex Med* 2007;**4**:218–25.
[25] Shaeer O. Implantation of penile prosthesis in cases of corporeal fibrosis: modified Shaeer's excavation technique. *J Sex Med* 2008;**5**:2470–6.
[26] Knoll LD, Fisher J, Benson Jr RC, Bilhartz DL, Minich PJ, Furlow WL. Treatment of penile fibrosis with prosthetic implantation and flap advancement with tissue debulking. *J Urol* 1996;**156**:394–7.

[27] Akin-Olugbade O, Parker M, Guhring P, Mulhall J. Determinants of patient satisfaction following penile prosthesis surgery. *J Sex Med* 2006;**3**:743–8.
[28] Djinovic R. Penile corporoplasty in Peyronie's disease: which technique, which graft? *Curr Opin Urol* 2011;**21**:470–7.
[29] Wang R, Howard GE, Hoang A, Yuan JH, Lin HC, Dai YT. Prospective and long-term evaluation of erect penile length obtained with inflatable penile prosthesis to that induced by intracavernosal injection. *Asian J Androl* 2009;**11**:411–5.
[30] Garaffa G, Sansalone S, Ralph DJ. Penile reconstruction. *Asian J Androl* 2013;**15**:16–9.
[31] Lue TF, El-Sakka AI. Lengthening shortened penis caused by Peyronie's disease using circular venous grafting and daily stretching with a vacuum erection device. *J Urol* 1999;**161**: 1141–4.
[32] Egydio P, Perovic SV, Sansalone S. Surgical treatment of severe Peyronie's disease for maximum penile length and girth gain. *J Urol* 2008;**179**(Suppl.):256.
[33] Ralph DJ, Minhas S. The management of Peyronie's disease. *BJU Int* 2004;**93**:208–15.
[34] Ralph D, Gonzalez-Cadavid N, Mirone V, Perovic S, Sohn M, Usta M, et al. The management of Peyronie's disease: evidence-based 2010 guidelines. *J Sex Med* 2010;**7**:2359–74.
[35] Kadioglu A, Sanli O, Akman T, Ersay A, Guven S, Mammadov F. Graft materials in Peyronie's disease surgery: a comprehensive review. *J Sex Med* 2007;**4**:581–95.