Arab Journal of Urology (2013) **11**, 272–277

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

www.sciencedirect.com

REVIEW

The pathophysiology of Peyronie's disease

Ahmed I. El-Sakka [a,*], **Emre Salabas** [b], **Murat Dinçer** [b], **Ates Kadioglu** [b]

[a] *Department of Urology, Suez Canal University, Ismailia, Egypt*
[b] *Department of Urology, Faculty of Medicine, Istanbul University, Turkey*

Received 4 May 2013, Received in revised form 9 June 2013, Accepted 9 June 2013
Available online 7 August 2013

KEYWORDS

Peyronie's disease;
Tunica albuginea;
Pathophysiology;
Fibrosis

ABBREVIATIONS

PD, Peyronie's disease;
ED, erectile dysfunction;
EF, erectile function (domain);
TA, tunica albuginea;
DM, diabetes mellitus;
GF, growth factor;
FGF, fibroblast GF;
ROS, reactive oxygen species;
(i)NOS, (inducible) nitric oxide synthase;
MMP, matrix metalloproteinase

Abstract ***Objective:*** To review the contemporary knowledge of the pathophysiology of Peyronie's disease (PD).

Methods: Medline was searched for papers published in English from 2000 to March 2013, using the keywords 'Peyronie's disease' and 'pathophysiology'.

Results: More than 300 relevant articles were identified for the purpose of this review. Unfortunately only a few studies had a high level of evidence, and the remaining studies were not controlled in their design. Many theories have been proposed to explain the cause of PD, but the true pathogenesis of PD remains an enigma. Identifying particular growth factors and the specific genes responsible for the induction of PD have been the ultimate goal of research over the past several decades. This would provide the means to devise a possible gene therapy for this devastating condition. We discuss present controversies and new discoveries related to the pathophysiology of this condition.

Conclusion: PD is one of the most puzzling diseases in urology. The pathogenesis remains uncertain and there is still controversy about the best management. The pathogenesis of PD has been explored in animal models, cell cultures and clinical trials, but the results have led to further questions. New research on the aetiology and pathogenesis of PD is needed, and which will hopefully improve the understanding and management for patients with this frustrating disease.

* Corresponding author. Address: Department of Urology, Faculty of Medicine, Suez Canal University, Round Road, 41111 Ismailia, Egypt. Tel.: +20 122 3456364; fax: +20 64 3200035.
E-mail address: aielsakka@yahoo.com (A.I. El-Sakka).

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.2013.06.006

Introduction

Peyronie's disease (PD) was first reported as *induratio penis plastica* in 1743 by Francois Gigot de la Peyronie, surgeon to King Louis XV of France. PD, while known by many synonyms, e.g., 'penile fibromatosis' and 'plastic induration of the penis', currently remains a therapeutic dilemma for physicians, even though it was initially described more than 250 years ago.

PD is a localised connective tissue disorder that primarily affects the tunica albuginea (TA) and the areolar space between the TA and erectile tissue [1]. It is characterised by the development of a circumscribed painless, dense, fibrous plaque, resulting in angulation of the erect penis in the direction of the plaque. The damage to self-esteem, reflecting on the patient's personal life, can make it a physically and psychologically debilitating disease. PD is not a rare condition, and reports indicate that up to 1% of men are affected. Most cases reported have been in white men, usually during the fifth and sixth decades of life, but there are reports of PD as early as the teenage years and into the ninth decade [2–4].

In a more recent investigation, El-Sakka [5] showed that PD is more prevalent than previously thought. The prevalence of PD was up to 8% in patients with erectile dysfunction (ED) who were screened for PD. Furthermore, there were significant associations between the risk factors for ED and PD, and with significant associations reported between PD and age, obesity, smoking, duration and number of cigarettes smoked per day. Dyslipidaemia, psychological disorders and the presence of at least one risk factor were significantly associated with PD. There were significant associations between a longer duration and poor metabolic control of diabetes and PD [6].

The effect of type 2 diabetes mellitus (DM) and PD, both alone and together, on the vascular status of erection in patients with ED was also assessed [7]. The mean scores of the erectile function (EF) domain of the International Index of Erectile Function (questions 3 and 4) were significantly lower in patients with both DM and PD than in those with either alone. Those with only DM had significantly lower mean scores for the EF domain than had patients with only PD. The mean peak systolic velocity and resistive index were significantly lower, and the mean end-diastolic velocity was significantly higher in patients with both DM and PD than in those with either condition alone. The authors concluded that type 2 DM and PD, both alone and together, compromised the vascular status of erection. Type 2 DM had the principal effect, but PD augmented the effect on erection and the variables assessed by Doppler ultrasonography.

On the natural history and prognosis of PD, Gelbard et al. [8] reported that there was some resolution of PD in 13% of patients, with 47% showing no change and gradual progression in 40%. The prognosis is particularly good when the patient is young and has a soft plaque (of < 2 cm), and when the duration of symptoms is brief. Penile deformity usually persists in patients who present with a substantial early penile angulation ($> 45°$). Moreover, the prognosis is poor when calcification develops within the plaque.

Pathogenesis and pathology

The anatomically-based hypothesis of PD

The arrangement of the vessels traversing the TA is unique. The arteries are cushioned by a cuff of loose areolar tissue, while the veins directly contact the fibrous tunica. If the fibres of the tunica are disrupted by a blunt trauma with extravasation, then the oedema and cell infiltration impinge on the adjacent venous channels and form a 'trapped' inflammatory response. The production of intercellular matrix and collagen fibres is then stimulated by secretions from leukocytes and macrophages, and the release of cytokines. Because the inflammation is constrained the cytokines cannot disperse and degrade, and they stimulate the production of more cytokines, which sequentially produce more matrix and collagen. PD can thus be considered as an aberrant wound-healing process in response to an inflammation constrained within the many layers of the TA [9].

The abnormalities associated with PD are attributable to the unique anatomy of the TA. The dense layers restrict the inflammation, venous outflow channels are compressed by oedema and cell infiltration, whilst the influx of leukocytes and macrophages continues because the arterial flow is not impeded. The end result is an excessive production of collagen fibres ascribed to a prolonged inflammatory response, with degradation of the delicate network of collagen and elastic fibres. Early in the process the inflammation and oedema can irritate the nerve endings, producing pain with or with no erection. The pain might abate when the inflammatory reaction matures or the trapped nerve fibres die. In the chronic phase, when the fibrosis begins to affect the erectile tissue, ED will be inevitable. These changes can contribute to the clinical presentation of PD, with an early phase comprising a triad of pain, plaque and penile deformity, and a late triad of plaque, penile deformity and ED [9].

The abnormal fibrotic reaction

The initiation of the disease is accepted as the extravasation of fibrinogen, converted to fibrin with the aid of thrombin, in the intralaminar space in the TA before the inflammation and fibrosis of both the plaque and normal-looking TA [10]. While fibrin deposition is

augmented by growth factors (GFs), e.g., fibroblast GF (FGF) and vascular endothelial GF, and the lack of fibrinolytic enzymes and vascular structure in the TA, the protein itself is a strong chemoattractant promoting the ingrowth of inflammatory cells (macrophages, neutrophils and mast cells), cytokines (TGF-β 1, etc.) and fibroblasts [11,12].

Fibroblasts proliferate and are attracted to the trauma site as a result of mediators such as platelet-derived GF, TNF-α, FGF and interleukin-1, the last two also induce collagen synthesis [13]. While interleukin-1 and TNF-α originate from monocytes and macrophages, respectively, there are high levels of FGF expression from the myofibroblasts in the plaque formations [14]. Myofibroblasts are mesenchymal cells combining contractile smooth muscle cells with collagen-synthesising fibroblasts [11].

Devine and Horton [15] hypothesised that PD is caused by an abnormal fibrotic reaction to minimal trauma. The TA is a laminated structure with two distinct layers, the outer longitudinal and the inner circular layer that fuse to form a median septum. Bending of the partially rigid penis can result in de-lamination of the TA in the area of stress, and cause microvascular trauma. In a partly rigid penis destabilisation of the axial erectile rigidity mechanism acts as a potential risk for buckling injury [16–18].

Such trauma causes de-lamination of the septal fibres, with bleeding into the intralaminal spaces. These early lesions are associated with a largely perivascular lymphatic and plasmacytic inflammatory cellular infiltrate in the areolar connective tissue sleeve below the TA [1].

In another experimental study, El-Sakka et al. [19] assessed whether a clean incisional trauma to the TA could produce PD-like condition. Such surgical trauma to the TA induced histological changes similar to those in the acute phase of PD, but not the overt pattern of the chronic phase of PD. It also caused an early but transient up-regulation of TGF-β1 protein expression in the rat penis. The authors concluded that surgical incisional trauma does not result in PD-like changes in the TA. These findings support the notion that entrapment of inflammatory cells and the deposition of extracellular matrix in the multi-layered structure of the TA is the key factor in inducing PD [20].

Electron microscopy, both transmission and scanning, showed that in normal TA the elastic fibres form an irregular lattice on which the collagen fibrils lie. These ultrastructural findings showed that the multilayered form of the TA seems to be distinct and can slide over the adjacent layers. In normal TA there is flexibility, but in PD plaques the collagen fibres are more closely packed and this ultimately causes tethering, and hence curvature of the penis towards the plaque [21,22].

Oxidative damage, autoimmunity, genetic and other unsettled theories

There is reportedly an increase in oxidative stress in fibrogenesis, and an increase in connective tissue disorders in chronic disease states of hepatic, pulmonary and nervous system tissue degeneration [23]. Free radicals such as superoxide, peroxynitrite and peroxide-generated species can result in lipid peroxidation and tissue damage, as well as stimulate connective tissue synthesis in fibroblasts and increased activity in the inflammatory process [22].

Vande Berg et al. [24] suggested that PD is an autoimmune response to vascular trauma. Several studies have also shown features of autoimmunity, in particular the cell-mediated response [25]. Stewart et al. [26] showed that antibodies to elastin are present in all patients with PD, and that there were increased serum levels of antitropoelastin (reflecting elastin synthesis) and anti-α-elastin (reflecting elastin destruction). Van de Water [12] noted that the two general mechanisms contributing to the generation of the wound extracellular matrix are the leakage of plasma proteins, such as plasma fibronectin and fibrinogen, and the synthesis of variants of fibronectin by wound cells. Although a familial tendency towards PD has been proposed, there are conflicting results on the association of HLA-B27 or HLA-B7 with the disease [27].

Gonzalez-Cadavid et al. recently reported that the levels of expression of TGF β 1 and pro-and anti-fibrotic gene products, and the ratio of nitric oxide to reactive oxygen species (ROS) in the TA, are apparently necessary for the formation and progression of the PD plaque, and affect the expression of several genes. Further assessment is possible with DNA-based chip arrays, and the results from the PD plaque are encouraging. The genes *OSF-1* (osteoblast recruitment), *MCP-1* (macrophage recruitment), and procollagenase IV (collagenase degradation), with other fibrotic genes, were identified as being possible candidate regulatory genes for PD [28].

Molecular mechanisms: cytokines and growth factors

Important factors in the pathogenesis of PD include the regulation of collagen synthesis by many endogenous and exogenous factors, particularly those that produce oxygen-free radicals, e.g., ascorbic acid, and other biologically active peptides like epidermal GF and insulin-like GF. TGF-β has recently received attention as a cytokine influencing the deposition of extracellular matrix, and inducing fibrosis in the TA [22,29,30]. TGF-β is also implicated as a cause of chronic fibrotic conditions, and is involved in many vital processes, including inflammation, stimulating the formation of intracellular matrix, fibroblast production, and normal healing [31].

Whilst increasing evidence suggests that TGF-β is a cytokine, vital for tissue repair, its overactivity might be responsible for the tissue damage caused by scarring in many serious diseases. The pathological sequelae of the actions of TGF-β have been referred to as the 'dark side' of tissue repair [32]. In the future, inhibitors of TGF-β could be significant as drugs for controlling these conditions [33].

In a study assessing the pathogenesis of PD [34] the authors showed that the high frequency of microsatellite alterations, and loss of heterozygosity, were associated with PD, suggesting their role in the pathogenesis of this disease.

El-Sakka et al. [30] confirmed the actions of TGF-β in the pathogenesis of PD using an animal model in which the progression of PD could be followed. This rat model produced cellular and molecular changes similar to those found in PD, which were invoked using an injection of cytomodulin, a synthetic haptapeptide with TGF-β like activity, into the TS of the rat penis. At 6 weeks after this injection 15 of 18 rats had tunical thickening and plaque formation, and increased expression of TGF-β1 mRNA and protein. There was no significant TGF-β 2 or TGF-β 3 protein expression.

The same group [35] also investigated the effect of colchicine on the histological and molecular changes in this rat model. The administration of colchicine soon after inducing the PD-like condition inhibited the expression of TGF-β and could prevent the development of fibrosis of the TA.

Furthermore, a study using this rat model [36] showed the activation of nuclear factor kappa b, a regulator of the expression of several genes, and that encodes for adhesion molecules, after an injection with TGF-β and injury to the rat penis. Isoforms of nitric oxide synthase (NOS), particularly the inducible form (iNOS), modulated the onset and progression of fibroblast production or wound healing. Inhibiting iNOS resulted in the greater deposition of collagen around the lesions induced by TGF-B1, suggesting that iNOS suppresses collagen production in PD [37,38].

'Tight skin' (*Tsk*) mice were used in a genetic animal model of PD, wherein fibrous plaque, penile curvature, chondroid metaplasia and ossification are apparent when there is up-regulation of TGF-β and iNOS genes mediated by hypoxic-inducible factor 1. The mutated *Fibrilin 1* gene is the key factor in this Tsk rat model, through the extracellular incorporation of microfibril-associated glycoprotein 2 and type I collagen, while iNOS is thought to be a counter-protective mechanism. The limitations of this model are that the disease is not progressive after 12 months, and that the fibrosis is systemic, affecting other organs and the corpus cavernosa, in addition to the TA [39].

Francisco et al. [40] proposed a new animal model for PD, in which a combination of TGF-β and tetradecyl sulphate is injected into the subtunica of mice. A palpable penile plaque and penile curvature, as well as a functional decrease in cavernosal pressures lasting for $\geqslant$9 weeks, were stated as the superior features of this model. A group of mice given a combined therapy had a better response than a group treated with only TGF-β 1, and this suggested an interesting area of work for the future medical treatment of PD.

The overexpression of myostatin, a member of TGF-β family, has been found in PD plaques, and it induced new plaque when induced, and condensed the plaque already formed by TGF-β 1 [41]. Other pro-fibrotic factors, such as plasminogen activation inhibitor-2 and ROS, as well as TGF-β 1, are released during the acute inflammation subsequent to trauma, and can be aggravated after transition to the chronic phase. A dense fibrotic plaque is apparent that can be accompanied by calcification and ossification of the plaque, as well as the presence of osteoblasts [42,43].

A proposed defence mechanism against the pro-fibrotic factors is iNOS, as it leads to NO release. The fibrin clot in the TA attracts monocyte chemotactic protein 1, which itself probably induces iNOS. This proposal is supported by the reverse correlation of pro-fibrotic factor levels and iNOS activity, regulated by gene transfer and L-N-(1-iminoethyl)-lysine acetate inhibition in animal experiments [43]. It was also claimed that NO reduces ROS activity, leads to apoptosis in myofibroblasts, and inhibits collagen synthesis (together with its product cGMP) [44]. There was a reduction in plaque size, oxidative stress and alpha-smooth muscle actin staining (a sign of myofibroblasts) in PD fibroblast cultures after administering a phosphodiesterase-5 inhibitor [45].

The inhibition and lack of collagenases contribute to the PD process, while iNOS, matrix metalloproteinases (MMP)-2 and -9, decorin (which binds TGF-β 1) and thymosins are the active defence mechanisms against the disease. The positive effect of decorin on the maximum cavernous pressure and the collagen organisation of the fibrotic penis was shown in a rat model, and this suggests a new therapy for the disease [46]. Furthermore, MMP-1, -8 and -13, which are inhibited by TGF β 1-induced tissue inhibitors of MMPs in PD, are able to renovate the normally lysis-resistant collagen I and III fibres [47]. The overexpression of TNF-related apoptosis-inducing ligand and its death receptor-5 was recently reported to occur in PD plaque when compared to normal TA, indicating the role of an external apoptotic pathway in plaque formation [48].

The persistence of myofibroblasts which are removed by apoptosis was investigated in a recent study in which the expressions of apoptotic genes were investigated (Fas, Fas Ligand, Bcl-2, p53, caspase 3 and 8). In that study there was a relative increase in apoptotic FAS ligands, with no parallel improvement in the FAS

receptors. In only 10 of 40 apoptotic genes (anti-apoptotic Bcl-2 genes) was an increase of more than 1.5-fold detected in PD plaques when compared with TA, while the expression of 13 genes was more than 1.5 times higher in normal TA. However, statistically insignificant results in PD plaques and control TA suggested that the plaque is not a localised disease of the TA, but rather it develops from the vulnerable regions of TA exposed to deleterious factor(s), with trauma being the prominent one [49].

In relation to the therapeutic benefits of understanding the pathophysiological mechanisms of PD, Jang et al. [50] reported that the overexpression of TGF-β and activation of Smad transcriptional factors are known to be crucial in the pathogenesis of PD. Thus inhibiting the TGF-β signalling pathway using ALK5 inhibitors might be a promising therapeutic strategy for treating PD. Both elastin and collagen are up-regulated by TGF-β 1 in TA-derived fibroblasts, and this probably contributes to the PD phenotype. Pretreatment with pentoxifylline attenuates both collagen fibre deposition and elastogenesis in TA-derived fibroblasts exposed to TGF-β 1 [51], and these effects suggest a useful role for pentoxifylline in the management of PD. Furthermore, the expression of elastin mRNA and protein is up-regulated in TA-derived fibroblasts by TGF-β 1. Pentoxifylline had no effect on elastin production, but attenuates elastogenesis in TA-derived fibroblasts through an Alpha-1 antitrypin-related mechanism [52].

Conclusions

PD is one of the most puzzling diseases in urology. The pathogenesis remains uncertain, and there are still controversies about the proper management of the condition. The pathogenesis of PD has been explored in animal models, cell cultures and clinical trials, but this has raised more questions. New research on the causes and pathogenesis is urgently needed and which hopefully will improve the management of patients with this frustrating disease.

Conflict of interest

There is no conflict of interest.

Source of funding

None.

References

[1] Smith BH. Peyronie's disease. *Am J Clin Pathol* 1966;**45**:670–8.
[2] Ludwig G. Evaluation of conservative therapeutic approachs to Peyronie's disease (fibrotic induration of the penis). *Urol Int* 1991;**47**:236–9.
[3] 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.
[4] Kadioglu A, Sanli O. In: Levine LA, editor. *Peyronie's disease: a guide to clinical management*. Totowa: Humana Press; 2007. p. 9–18.
[5] El-Sakka AI. Prevalence of Peyronie's disease among patients with erectile dysfunction. *Eur Urol* 2006;**49**:564–9.
[6] El-Sakka AI, Tayeb KA. Peyronie's disease in diabetic patients being screened for erectile dysfunction. *J Urol* 2005;**174**:1026–30.
[7] El-Sakka AI, Tayeb KA. Vascular impairment of erection in patients with diabetes and Peyronie's disease: is that accumulative? *J Sex Med* 2009;**6**:1736–42.
[8] Gelbard MK, Dorey F, James K. The natural history of Peyronie's disease. *J Urol* 1990;**144**:1376–9.
[9] Lue TF. Peyronie's disease. An anatomically-based hypothesis and beyond. *Int J Impotence Res* 2002;**14**:411–3.
[10] Costa WS, Rebello SB, Cardoso LE, Cavalcanti AG, Sampaio FJ. Stereological and biochemical analysis of muscular and connective tissue components in the penile corpus cavernosum adjacent to the fibrous plaque of Peyronie's disease. *BJU Int* 2009;**103**:212–6.
[11] Diegelmann RF. Cellular and biochemical aspects of normal and abnormal wound healing: an overview. *J Urol* 1997;**157**:298–302.
[12] Van de Water L. Mechanisms by which fibrin and fibronectin appear in healing wounds: implications for Peyronie's disease. *J Urol* 1997;**157**:306–10.
[13] Moreland RB, Nehra A. Pathophysiology of Peyronie's disease. *Int J Impot Res* 2002;**14**:406–10.
[14] Mulhall JP, Thom J, Lubrano T, Shankey TV. Basic fibroblast growth factor expression in Peyronie's disease. *J Urol* 2001;**165**:419–23.
[15] Devine CJ, Horton CE. Peyronie's disease. *Clin Plast Surg* 1988;**15**:405–9.
[16] El-Sakka AI. Pathophysiology of Peyronie's disease. *J Sex Med News Bull* 2005;**16**:27–9.
[17] Devine Jr CJ. Introduction: international conference on Peyronie's disease advances in basic and clinical research. March 17–19, 1993. *J Urol* 1997;**157**:272–5.
[18] Somers KD, Dawson DM. Fibrin deposition in Peyronie's disease plaque. *J Urol* 1997;**157**:311–5.
[19] El-Sakka AI, Selph CA, Yen TSB, Dahiya R, Lue TF. The effect of surgical trauma on rat tunica albuginea. *J Urol* 1998;**159**:1700–7.
[20] Akkus E, Carrier S, Baba K, Hsu GL, Padma-Nathan H, Nunes L, et al. Structural alterations in the tunica albuginea of the penis: impact of Peyronie's disease, ageing and impotence. *Br J Urol* 1997;**79**:47–53.
[21] Brock G, Hsu GL, Nunes L, von Heyden B, Lue TF. The anatomy of the tunica albuginea in the normal penis and Peyronie's disease. *J Urol* 1997;**157**:276–81.
[22] El-Sakka AI, Hassan MU, Nunes L, Bhatnagar RS, Yen TSB, Lue TF. Histological and ultrastructural alterations in an animal model of Peyronie's disease. *Br J Urol* 1998;**181**:445–52.
[23] Poli G, Parola M. Oxidative damage and fibrogenesis. *Free Radic Biol Med* 1997;**22**:287–305.
[24] Vande Berg JS, Devine CJ, Horton CE, Smoers KD, Wright Jr MS, Leffell MS, et al. Mechanisms of calcifications in Peyronie's disease. *J Urol* 1982;**127**:52–4.
[25] Ralph DJ, Mirakian R, Pryor JP, Bottazzo GF. The immunological features of Peyronie's disease. *J Urol* 1996;**155**:159–62.
[26] Stewart S, Malto M, Sandberg L, Colburn KK. Increased serum levels of anti-elastin antibodies in patients with Peyronie's disease. *J Urol* 1994;**152**:105–6.
[27] Leffell MS. Is there an immunologic basis for Peyronie's disease ? *J Urol* 1997;**157**:295–7.

[28] Gonzalez-Cadavid NF, Magee TR, Ferrini M, Qian A, Vernet D, Rajfer J. Gene expression in Peyronie's disease. *Int J Impot Res* 2002;**14**:361–74.
[29] El-Sakka AI, Hassoba HM, Pillarisetty RJ, Nunes L, Dahiya R, Lue TF. Peyronie's disease is associated with an increase in transforming growth factor beta protein expression. *J Urol* 1997;**158**:1391–4.
[30] El-Sakka AI, Hassoba HM, Chui RM, Bhatnagar RS, Dahiya R, Lue TF. An animal model of Peyronie's-like condition associated with an increase of transforming growth factor beta mRNA and protein expression. *J Urol* 1997;**158**:2284–90.
[31] Sporn MB, Roberts AB, Wakefield LM, de Crombrugghe B. Some recent advances in the chemistry and biology of transforming growth factor-Beta. *J Cell Biol* 1987;**105**:1039–45.
[32] Border WA, Ruoslahti E. Transforming growth factor-b in disease. The dark side of tissue repair. *J Clin Invest* 1992;**90**:1–7.
[33] Castilla A, Prieto J, Fausto N. Transforming growth factors b1 and a in chromic liver disease. *N Engl J Med* 1991;**324**:933–40.
[34] Perinchery G, El-Sakka AI, Angan A, Nakajima K, Dharia A, Tanaka Y, et al. Microsatellite alterations and loss of heterozygosity in Peyronie's disease. *J Urol* 2000;**164**:842–6.
[35] El-Sakka AI, Bakircioglu ME, Bhatnagar RS, Yen TSB, Dahiya TF, Lue TF. The effects of colchicine on a Peyronie's like condition in an animal model. *J Urol* 1999;**161**:1980–3.
[36] Bivalacqua TJ et al. Potential role of nuclear factor-kB in the induction of Peyronie's-like condition in the rat. *J Urol* 1999;**161**:781A.
[37] Bivalacqua TJ, Diner EK, Novak TE, Vohra Y, Sikka SC, Champion HC, et al. A rat model of Peyronie's disease associated with a decrease in erectile activity and an increase in inducible nitric oxide synthase protein expression. *J Urol* 2000;**163**:1992–8.
[38] Bivalacqua TJ, Champion HC, Leungwattanakij S, Yang DY, Hyun JS, Abdel-Mageed AB, et al. Evaluation of nitric oxide synthase and arginase in the induction of a Peyronie's-like condition in the rat. *J Androl* 2001;**3**:497–506.
[39] Lucattelli M, Lunghi B, Fineshi S, Mirone V, D'Emmanuele di Villa Bianca R, et al. A new mouse model of Peyronie's disease: an increased expression of hypoxia inducible factor-1 target genes during the development of penile changes. *Int J Biochem Cell Biol* 2008;**40**:2638–48.
[40] Francisco G, Ling DY, Chung E, Brock M, Brock GA. Novel rat model for Peyronie's disease that demonstrates durability and functional detriments. *CUA J* 2012;**6**(Suppl. 1) [Abstract, MP-06.02].
[41] Cantini LP, Ferrini MG, Vernet D, Magee TR, Quian A, Gelfand RA, et al. Pro-fibrotic role of myostatin in Peyronie's disease. *J Sex Med* 2008;**5**:1607–22.
[42] Gonzalez-Cadavid NF, Rajfer J. Experimental models of Peyronie's disease. Implications for new therapies. *J Sex Med* 2009;**6**:303–13.
[43] Gonzalez-Cadavid NF, Rajfer J. Mechanisms of disease. New insights into the cellular and molecular pathology of Peyronie's disease. *Nat Clin Pract Urol* 2005;**2**:291–7.
[44] Vernet D, Ferrini MG, Valente E, Magee TR, Bou-Gharios G, Rajfer J, et al. Effect of nitric oxide on the differentiation of fibroblasts into myofibroblasts in the Peyronie's fibrotic plaque and in its rat model. *Nitric Oxide* 2002;**7**:262–76.
[45] Valente EG, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid NF. L-arginine and PDE inhibitors counteract fibrosis in Peyronie's plaque and related fibroblast cultures. *Nitric Oxide* 2003;**9**:229–44.
[46] Akman T, Tefekli A, Armagan A, Kiliçaslan I, Ozerman B, Tepeler A, et al. Decorin as a new treatment alternative in Peyronie's disease: preliminary results in the rat model. *Andrologia* 2013;**45**:101–6.
[47] Chung E, De Young L, Solomon M, Brock GB. Peyronie's disease and mechanotransduction. An in vitro analysis of the cellular changes to Peyronie's disease in a cell-culture strain system. *J Sex Med* 2013;**10**:1259–67.
[48] Loreto C, Barbagli G, Djinovic R, Vespasiani G, Carnazza ML, Miano R, et al. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and its death receptor (DR5) in Peyronie's disease. A biomolecular study of apoptosis activation. *J Sex Med* 2011;**8**:109–15.
[49] Zorba OU, Sirma S, Ozgon G, Salabas E, Ozbek U, Kadioglu A. Comparison of apoptotic gene expression profiles between Peyronie's disease plaque and tunica albuginea. *Adv Clin Exp Med* 2012;**21**:607–14.
[50] Jang JH, Ryu JK, Suh JK. Activin receptor-like kinase 5 inhibitor attenuates fibrosis in fibroblasts derived from Peyronie's plaque. *Korean J Urol* 2012;**53**:44–9.
[51] Shindel AW, Lin G, Ning H, Banie L, Huang YC, Liu G, et al. Pentoxifylline attenuates transforming growth factor-β 1-stimulated collagen deposition and elastogenesis in human tunica albuginea-derived fibroblasts part 1: impact on extracellular matrix. *J Sex Med* 2010;**7**:2077–85.
[52] Lin G, Shindel AW, Banie L, Ning H, Huang YC, Liu G, et al. Pentoxifylline attenuates transforming growth factor-beta1-stimulated elastogenesis in human tunica albuginea-derived fibroblasts part 2. Interference in a TGF-beta1/Smad-dependent mechanism and downregulation of AAT1. *J Sex Med* 2010;**7**:1787–97.