REVIEW

All about Peyronie's disease

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Abstract   Peyronie's disease (PD) is an acquired connective tissue disorder of the tunica albuginea of the corpus cavernosum, characterized by excessive fibrosis and plaque formation. PD can result in significant physical and psychological morbidity; as it may prevent intercourse and cause adverse impacts on partner relationships. The exact etiology and pathophysiology remain unclear, and many misconceptions about the disease associations, course and treatment exist.

The disease has two distinct stages. The acute stage is characterized by pain, and disease may progress during this stage. Non-surgical managements at this stage aim to alleviate pain and stabilize the disease. Results for non-surgical treatment are often conflicting. The chronic stage occurs 6—12 months later, where pain disappears and the deformity stabilizes. Surgical treatment is reserved for significant deformity or with inability to penetrative intercourse. The choice of the surgical technique depends on the length of the penis, degree of deformity, erectile function, patients' expectations and surgeon's preference.

1. Etiology and pathophysiology

Peyronie's disease (PD) is an acquired connective tissue disease of the tunica albuginea of the corpus cavernosum, characterized by excessive fibrosis and plaque formation, which do not expand like the normal tunica albuginea causing penile deformities in the erect state including curvature, shortening, indentation and narrowing with a hinge effect [1,2]. PD can result in significant physical and psychological morbidity. Men may suffer from penile pain, deformities and erectile dysfunction (ED) that prevent sexual intercourse and reduce satisfaction, with adverse impacts on partner relationships [3].

Recent reports showed that the prevalence of PD may be up to 9%. However, the true prevalence may be under-reported as some men may not seek medical advice due to embarrassment or as a result of the false belief that the condition is untreatable [4]. It typically affects males between 45 and 60 years [5]. However, 10% of patients who

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present with PD are younger than 40 years, including teenagers [6,7]. Younger patients are more likely to present earlier in the disease course, have pain, and more likely to progress [8]. It is more common in younger Caucasian men and after radical pelvic surgery, namely radical prostatectomy [9]. PD is commonly associated with some comorbid conditions and risk factors including diabetes, hypertension, hyperlipidemia, ED, smoking, and excessive consumption of alcohol [8,10,11]. PD occurs in 8% of type 2 diabetes mellitus patients [12], 16% of patients who had radical prostatectomy [9], and 20% of patients who have both diabetes and ED [13]. Men with PD usually suffer significant distress and nearly half of men with PD have mild or moderate depression [14,15]. Patients with PD are concerned about their sexual attractiveness, self-image, sexual functioning and performance. Anxiety, depression, low self-esteem and relationship disorders were reported in more than half of the patients [3,14—16]. The degree of distress does not necessarily correlate with the degree of penile curvature or deformity [15]. The natural history of PD varies; penile curvature worsens in 30%—50% of patients, stabilizes in 47%—67%, while spontaneous improvement may occur in 3%—13% of patients [8,16,17].

Misconceptions about PD are very common, especially among general practitioners, who are usually the initial encounters of PD cases [4]. Common misconceptions include the underestimation of PD, and the assumption that it is only a disease of the elderly. Many believe that it is not associated with ED and that no treatment is available, or it will resolve for sure with time [4]. These misconceptions represent obstacles to early treatment in the disease course. Studies showed that earlier age of presentation (40—50 years) and the presence of hypertension, diabetes mellitus and dyslipidemia pose a greater risk for early disease progression [8]. Studies suggest also that early detection and treatment may reduce psychological distress [4]. Therefore, greater awareness of the natural history and course of PD may promote early detection and prompt treatment of the disease, and improve physical and psychological outcomes in these men [4].

The exact etiology of PD is unknown. The most widely accepted theory is trauma or repeated microtrauma to the erect penis in genetically susceptible individuals. Repeated microvascular traumatic injury to the tunica albuginea causes inflammation, disruption of the elastic fibers and deposition on fibrin [18,19]. This theory is also supported by epidemiologic association of PD with some traumatic events [20]. Some studies suggested that vascular trauma leads to osteoid formation via osteoblast like cells originating from the vascular lumen [20]. More recent reports showed that upregulation of certain genes, namely, *osteoblast specific factor 1*, may be responsible for plaque calcification [21]. Another theory is cavernosal hypoxia, which induces collagen deposition and fibrosis. This may explain the penile morphological changes and the development of PD following radical prostatectomy [9].

Multiple pathways have been suggested although the exact pathophysiology of PD remains unclear. PD has two phases that may be distinguished by symptom presentation. It starts with an acute inflammatory process characterized by increased proliferation of the tunical fibroblasts, some of which differentiate into myofibroblasts, with excessive deposition of collagen. The transforming growth factor (TGF)-β1 may play an important role in induction of collagen production by fibroblasts/myofibroblasts in the development of PD plaques [19,22]. Animal studies have shown that TGF-β1 enhances collagen deposition and plaques formation, while on the other hand suppressors of TGF-β1 caused regression of the plaques [23,24]. Moreover, overexpression of TGF-β1 was found in tissue samples from human PD plaque [25]. The association of PD with Dupuytren's contracture (in 20%—40% of cases) suggests a common fibro-proliferative disorder [10,26]. The hallmark of this stage is pain, which may occur either in the flaccid state or as painful erections. It typically resolves after 12—18 months of the disease onset [17].

The second is the chronic or fibrotic phase. It usually begins approximately 12—18 months following disease onset. Pain typically disappears, and plaque and penile deformity stabilize. At this stage, penile curvature and deformity rarely improve [17]. One study found that PD deformity stabilization was more likely among older patients and those who presented in the first 6 months of symptoms, while improvement rates were higher among younger patients [27]. Prolonged inflammation causes formation of dense fibrotic plaques, which may progress to calcification or ossification. The exact mechanism by which tissue mineralization occurs remains uncertain [28]. Calcification may be considered dystrophic in nature and may result in penile curvature [19,29]. The incidence of calcification currently varies widely, and most reports correlated the presence of plaque calcification to disease stabilization and severity [30]. In this context, improvement of deformities can occur in the early stages of the disease prior to dense calcification of the plaques [31]. However, a recent study found that calcified plaques were detected as early as 6 weeks following the onset of symptoms, suggesting that it does not occur exclusively in the setting of chronic or severe PD [29].

Some reports showed that patients with calcified plaques are less responsive to non-surgical treatment modalities and are more likely to progress to surgery [30,32,33]. However, these studies stratified patients according to the presence of calcification or not rather than its extent. One interesting study stratified patients according to the maximum dimension of calcifications as they appear on penile ultrasound; grade 1 (punctate or ≤0.3 cm), grade 2 (>0.3 cm and <1.5 cm) and grade 3 (≥1.5 cm or ≥2 plaques >1.0 cm) [29]. This study demonstrated that not all patients with calcified plaques will need surgery, while those with higher grades of calcification were more likely to have surgery. Hence, stratifying patients according to the extent of calcification may help prevent premature surgical intervention and may serve as a clinical tool to counsel patients on the odds of having surgery. This study also found that plaque calcification was associated with older age, penile deformity, and pain [29].

2. Diagnosis

History and physical examination usually are satisfactory for diagnosis. Symptoms usually differ according to the disease phase, which will impact the decision for medical

treatment and the timing for surgical intervention. In the acute or the active stage of the disease, patients usually report pain during erection. Pain is present in 35%–45% of patients during the early stages of the disease, and usually resolves during the first 12 months in more than 90% of patients [10]. Also, patients may report a recent change in penile curvature. The European guidelines recommend an objective assessment of penile curvature during erection, either by a home (self) photograph of a natural erection or using a vacuum-assisted erection test or an intracavernosal injection using vasoactive agents [10]. Risk factors for PD (diabetes, hypertension, dyslipidemia, smoking, and alcohol consumption) as well as the psychological burden caused by the disease should also be determined.

ED is a common association in more than half of men with PD. Erectile function can be assessed using validated instruments such as the International Index of Erectile Function (IIEF) [34]. It is crucial to assess erectile function and elucidate the exact timing in relation to the onset of PD, as this my influence further management of the patient [35]. It may occur as a result of penile pain during erection, functional disability as a result of the curvature or deformities, or due to psychological causes (performance anxiety and fear of partner rejection) [16]. Arteriogenic ED can still be detected, but veno-occlusive dysfunction remains the main cause of erectile dysfunction in PD [36]. Sexual dysfunction may worsen over the natural course of the disease [16].

The examination should start with a routine genitourinary assessment. The penis should be examined for palpable nodules or plaques, whose length should be measured at full stretch and during erection. Also, assessment of the penile length, rigidity, girth and curvature should also be done during erection [10,31]. General examination should include the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia [17], common associations with PD [10]. The end of the acute phase is usually not easy to elucidate, but resolution of pain and stability of the curvature for at least 3 months are well accepted criteria of disease stabilization, and to undertake surgical treatment if needed [16].

Among imaging modalities that have been described in the literature, penile duplex ultrasonography remains the preferred method of examination. It visualizes penile tissues and detects areas of calcification. It is also a valuable tool for hemodynamic assessment, as ED is a common association with PD [31]. Although ultrasonographic measurement of the plaque's size is operator dependent and is not recommended in the everyday clinical practice [10,37], a recent study suggested that sorting patients according to the extent of calcification of the plaques may be a valuable tool in counseling and prognostication of patients with PD [29].

3. Treatment

Determining the appropriate treatment depends on a variety of factors: the stage of the disease, the presence of pain, severity and direction of the curvature, penile length, and patient's erectile status [4]. Optimal patient management requires early detection and/or referral, to improve functional and psychological outcomes. Non-Surgical treatments may be considered for patients in the acute stage of the disease. Surgery is typically reserved for patients with stable disease [4].

3.1. Non-surgical treatment

Non-surgical treatment of PD targets the disease at the early stage. It aims at alleviating penile pain, decreasing disease progression, stabilizing inflammation, penile plaque and deformity [38]. It includes oral pharmacotherapy, intralesional injection therapy, and other topical treatments. The results of the studies on conservative treatment are often contradictory, complicating the process of patient counseling and decision making. Although preliminary results for most of these therapies were promising, data from randomized placebo-controlled studies failed to show any benefit for many of them [10].

3.1.1. Oral treatment
3.1.1.1. Vitamin E. Vitamin E acts as a natural antioxidant to reduce the number of oxygen-free radicals produced during cellular metabolism. It is very popular among urologists being available, safe and cheap. Despite its popularity in the treatment of PD, a double blinded placebo-controlled study failed to demonstrate any value in reduction of plaque size or improvement of deformity [10].

3.1.1.2. Potassium para-aminobenzoate (Potaba). Potaba decreases penile fibrosis by increasing oxygen uptake by the tissues, enhancing the secretion of glycosaminoglycans, and stimulating the activity of monoamine oxidases [39]. An early prospective double-blinded controlled study showed that Potaba significantly reduced penile pain but not penile curvature or penile plaque size [40]. In a more recent prospective randomized, double-blind, placebo-controlled study, it was effective in decreasing penile plaque size and stabilizing the penile curvature [41]. Side effects reported include nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty concentrating [10].

3.1.1.3. Tamoxifen. Tamoxifen is a non-steroidal estrogen receptor antagonist which is thought to modulate the secretion of TGF-β1 secretion by fibroblasts. A placebo-controlled, randomized study involving patients with advanced disease failed to show any significant improvement in pain, curvature, or plaque size in patients with PD [42].

3.1.1.4. Colchicine. Colchicine is believed to be beneficial in PD due to its anti-inflammatory effects. Studies showed significant improvement in penile pain and curvature, with reduction or disappearance of penile plaques [43,44]. A combination of vitamin E and colchicine proved valuable in early stage disease, with significant improvement in plaque size and curvature [45]. Reported side effects include gastrointestinal effects (nausea, vomiting, diarrhea) that can be improved with dose escalation [44].

3.1.1.5. Acetyl esters of carnitine. Acetyl esters of carnitine reduce penile fibrosis via decreasing intracellular

calcium levels. Hence, they suppress fibroblast proliferation and collagen production [46]. In a randomized, double-blind study, acetyl-L-carnitine proved to be more effective than tamoxifen with regards pain and curvature improvement, and similar in decreasing the size of plaques. Additionally, it showed also fewer side effects [47].

3.1.1.6. Pentoxifylline

3.1.1.6. Pentoxifylline. Pentoxifylline is a non-specific phosphodiesterase inhibitor which inhibits TGF-β1 and increases nitric oxide which appears to improve penile curvature and stabilizes the process of mineralization within the plaques [10]. Although the exact pathway by which it stabilizes or decreases the mineralization is still unclear, one study showed that it has no effect on elastin production, but diminishes elastogenesis in tunica albuginea-derived fibroblasts through an α1 antitrypsin-dependent mechanism [48]. Moreover, pentoxifylline may increase the microcirculation in the site of fibrotic and calcified plaques, which may lead to a more rapid plaque resolution and improvement in calcification over time [49]. Improvement or stabilization in calcium burden occurred in 92% of men treated withpentoxifylline, and these men were also less likely to report subjective worsening of their deformity [49]. Undesirable effects are generally mild and include nausea, dizziness, and headache [50].

3.1.1.7. Phosphodiesterase type 5 inhibitors (PDE5I). There is a growing evidence for the beneficial effect of PDE5I in PD. PDE5I may act by decreasing the ratio of collagen to smooth muscles [51]. It can also augment the effect of extracorporeal shock wave therapy (ESWT) on erectile function in patients with PD [52].

3.1.1.8. Other oral therapies. Coenzyme Q10 is a fat-soluble, vitamin-like quinine that is a powerful, endogenously secreted antioxidant. In a randomized control trial, it showed statistically significant improvement in the IIEF score, mean plaque area, and penile curvature at 6 months [53].

Omega-3 fatty acids (eicosapentonoic acid and docosahexonoicacid) inhibit the release of inflammatory mediators and enhance collagenase activity. However, in a randomized controlled trial it failed to show any benefit over placebo [54].

3.1.2. Intralesional treatment

Another option is to directly inject the pharmacological agent into the penile plaques. This ensures higher concentration inside the plaques while avoiding systemic side effects.

3.1.2.1. Clostridial collagenase (Xiaflex™). Clostridial collagenase is a purified bacterial enzyme that selectively breaks down collagen [55]. It is the only pharmacological agent available that can break down the plaques and therefore, improves the deformity. Xiaflex™ (collagenase of *Clostridium histolyticum*, a product of Auxilium Pharmaceuticals, Inc.) is only available through a Food and Drug Administration (FDA) restricted program under a Risk Evaluation and Mitigation Strategy (REMS), with trained healthcare professionals. Treatment course constitutes a maximum of four cycles; each consists of two injections and a penile modeling procedure. Within each cycle, there should be a period of 1—3 days between each injection, and between the second injection and the penile modeling procedure (aiming at relieving the curvature deformity and straightening the penis). The interval between cycles should be around 6 weeks [56]. The injection procedure starts with marking the target area of PD plaque in the erect state. The injection itself should be done while the penis is flaccid, where 0.58 mg is injected into the target plaque. This is repeated 1—3 days later for the second injection, and then followed by penile modeling procedure after further 1—3 days [56].

In previous studies, intralesional injection of clostridial collagenase reduced penile plaques size and deformity significantly especially for smaller plaques [57]. It was found to be effective in improving the deformity in patients with hourglass deformity, dorsal, and dorso-lateral curvatures but not ventral ones. In a double-blinded, placebo-controlled study, Clostridial collagenase improved plaque size and penile curvature in one third of the patients (in comparison to only 4% in the placebo group) [57]. Better response was achieved in patients with angulation less than 60° and plaque size smaller than 4 cm [57]. Adverse effects include penile pain, contusions, ecchymosis, swelling, redness and itching at or around the injection site [10].

3.1.2.2. Steroids. Intralesional steroids exert an anti-inflammatory action via inhibition of phospholipase A2, suppression of the immune response, and decreasing collagen synthesis [10]. However, no statistically significant improvement in deformity, plaque size or pain was encountered in a single-blind, placebo-controlled study [10]. Undesirable effects include thinning of the skin and immunosuppression [58].

3.1.2.3. Verapamil. Verapamil is a calcium channel blocker which inhibits the transport of extracellular matrix proteins as collagen, fibronectin, and glycosaminoglycans. It also enhances collagenases and inhibits fibroblasts proliferation [59]. It may be useful for the treatment of acute phase to stabilize disease progression or possibly reduce penile deformity. Results from a single-blinded, placebo-controlled study showed that at 6 months, plaque size decreased significantly with a trend towards improvement in penile curvature. Men with non-calcified plaques, plaques smaller than 2.5 cm, angulation deformity less than 30°, and disease duration less than 2 years showed a better response to intralesional verapamil [60]. Minor side effects were reported including nausea, light headedness, penile pain, and ecchymosis [10,61].

3.1.2.4. Interferon. Interferon-α2b inhibits fibroblast proliferation and collagen production. Additionally, it is thought to improve the healing of plaques [62]. Previous studies showed its value in the improvement of pain, plaque size and penile curvature [63]. A single-blinded, placebo-controlled study showed that after over 12 weeks

it demonstrated significantly improved plaque size (55% improvement) and penile curvature (27% improvement) in treated patients when compared to placebo [64]. Side effects include myalgia, arthralgia, sinusitis, fever and flu-like symptoms [10].

3.1.3. Topical treatments
3.1.3.1. Topical verapamil. Topical verapamil gel significantly diminished penile curvature, plaque size, and penile pain, especially when applied for 6 months [65].

3.1.3.2. Iontophoresis (transdermal electromotive drug administration [EMDA]). Studies showed improvement of penile curvature, plaque size and penile pain during erection [66]. In a randomized, double-blind, controlled study, a combination of iontophoresis, verapamil 5 mg and dexamethasone 8 mg resulted in improvement of penile curvature and plaque size [67]. This method is not known to be associated with any significant adverse event. Similarly, a double-blinded, placebo-controlled trial of iontophoresis, with and without verapamil, showed similar results between the two groups. This study demonstrated an improvement of 50% or more in penile deformity, suggesting that the electrical energy alone may be beneficial [67].

3.1.3.3. ESWT. There are two hypotheses for the mechanism of action of ESWT in PD: shock waves may cause damage of the penile plaque then induce remodeling; or it enhances the vascularity of the area by induction of an inflammatory reaction, increasing macrophage activity and plaque destruction and absorption [68]. In a prospective, randomized, double-blind, placebo controlled study, it was associated with significant improvement in penile pain but without improvement in penile curvature or mean plaque size [69,70].

3.1.3.4. Traction devices. The concept is based on over-stretching of the penile plaques, which causes an increase in the degradative enzymes and loss of the tensile strength and increased solubility, followed by remodeling [71]. One study showed an improvement in penile curvature, stretched penile length and erect girth in all men with no adverse side effects or skin complications [72]. No recommendations can be made based on the current evidence.

3.1.3.5. Vacuum devices. Vacuum devices have the same principles as traction devices. The use a vacuum device improved penile pain, increased the stretched penile length with an average of 0.5 cm, reduction of the curvature in most of men [73].

3.2. Surgical treatment

When medical treatment fails to correct the deformity, surgical treatment can be considered. Surgery aims at the correction of curvature, maintaining satisfactory penile length and rigidity to allow penetrative intercourse [4]. Surgery should be done only for patients with stable disease for at least 12 months, although 3 months have been also suggested [1,74,75]. Potential risks of surgery include penile shortening, ED (higher risk with penile lengthening procedures [1,76]), penile numbness, recurrent curvature (due to surgery before disease stabilization, reactivation of the condition, or the use of absorbable sutures [76]), the potential for palpation of knots and stitches below the skin, and the potential need for circumcision at the time of surgery [1].

Procedures for correction of curvature due to PD are either penile shortening or penile lengthening procedures [76]. Penile shortening procedures are performed on the convex (longer) side of the penis, while penile lengthening procedures are performed on the concave (shorter) side of the penis and require the use of a graft. The latter are commonly used to avoid excessive penile shortening, or to correct complex deformities [10]. The standard principles of surgery for correction of PD include peniledegloving, which may be combined with circumcision in many cases to avoid post-operative phimosis [76]. Penile prosthesis should be considered in PD associated with ED refractory to medical treatment [77]. The choice of the surgical technique depends on a number of factors, including penile length, location and degree of curvature, erectile function, patient goals and surgeon preference [1,4].

3.2.1. Penile shortening procedures
3.2.1.1. Nesbit technique. It involves removal of 5—10 mm transverse ellipses from the tunica albugineaor approximately 1 mm for each 10° of curvature [78,79]. The results of the Nesbit operation are excellent, where more than 80% of men have complete straightening of the penis after the procedure, with low risks for penile hypesthesia or recurrence of penile deformity [80]. However, penile shortening is the most commonly reported complication [81], which is 1—1.5 cm in most of the cases, with no gross impact on sexual intercourse [79,82]. Additionally, the actual degree of shortening is usually less than that perceived by the patient. Hence, the importance of documenting the pre-operative penile length [80,81]. One modification of the Nesbit procedure has been proposed, where partial thickness of the tunica albuginea is done instead of complete excision of a wedge from it [83].

3.2.1.2. Penile plication procedures. Results of the plication procedures and satisfaction rates are very similar to the Nesbit procedure [76]. Penile plication procedures have the same principle as the Nesbit but are simpler to perform. They are based on single or multiple longitudinal incisions on the convex side of the penis, which are then closed transversely (Heineke-Miculicz principle), or plication without making any incision, or '16 dot' technique [10]. The use of non-absorbable sutures may decrease the failure rates [10].

3.2.2. Penile lengthening procedures
They involve incision of the short concave side of the penis, lengthening it and creating a tunical defect, which is then filled with a graft. Lengthening procedures provide a reasonable choice for men with higher degree of curvature (more than 60°) and for those with hourglass deformity [10]. Postoperative erectile dysfunction (as high as 25%) is a common sequela due to venous leak [84]. Other

complications include graft contracture, which is results in the need for another surgery in about 17% of cases [85], and penile shortening (although the risk is significantly less compared with the aforementioned penile shortening procedures) [76]. Many grafting materials and techniques have been proposed, but the ideal graft material is yet to be determined (Table 1). One study showed that the presence of pre-operative ED, larger graft size, age older than 60 years, and ventral curvature were associated with poor functional outcome after grafting surgery [77].

Autologous grafts include saphenous vein, dermis, tunica vaginalis, buccal mucosa, rectus fascia, temporalis fascia and fascia lata [4,10]. *Vein graft*, saphenous vein is the most common vein graft used, followed by the dorsal vein of the penis [76]. Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to the underlying cavernosal tissue. However, complications reported include recurrent curvature (20%), penile shortening (17%) and graft herniation (5%) [10]. The use of *Tunica vaginalis* has several potential advantages; it is relatively avascular, easy to harvest and has a lower risk of contracture [86]. Contracture is a common complication for *Dermal grafts*, which result in recurrent penile curvature and penile shortening, with the need of surgical intervention in 17% of cases at 10 years [87]. Disadvantages of autologous grafts include additional donor-site morbidity and increased operative time. Their outcomes are no better than the more readily available allografts or xenografts [88].

Allografts include cadaveric tissues as pericardium, fascia lata, dura, and dermis [10]. Using c*adaveric pericardium, r*ecurrence of curvature occurred in 44% of patients. However, most men in this study were satisfied and reported successful sexual intercourse [87]. Xenografts, as porcine s*mall intestinal submucosa*, provide a scaffold for regeneration of host cells, and enhance angiogenesis and remodeling. Although promising, no sufficient data are available for any recommendations [89]. Synthetic materials are less favorable due to the increased risk of infections [4].

Table 1 Different types of grafts used in penile lengthening procedures for surgical treatment of PD [10].

Type	Grafts
Autologous grafts	Dermis
	Vein grafts
	Tunica vaginalis
	Temporalis fascia
	Rectus fascia
	Buccal mucosa
Allografts	Cadaveric pericardium
	Cadaveric fascia lata
	Cadaveric dura matter
	Cadaveric dermis
Xenografts	Porcine small intestinal submucosa
	Bovine pericardium
	Porcine dermis
Synthetic grafts	Gore-Tex
	Dacron

3.2.3. Penile prosthesis

Penile prosthesis implantation is done for men with PD associated with ED, which is refractory to PDE5I [76]. It acts as a tissue expander that will correct the curvature in few months [90]. Implantation of a penile prosthesis may be done with or without straightening maneuvers [1,38]. In a minority of patients, with high degrees of curvature, penile prosthesis implantation may be combined with penile shortening or lengthening procedures to achieve complete correction of the curvature [10]. The risk of complications following penile prosthesis implantation is the same as the general population [10].

3.2.4. Summary of the surgical treatment

Assessment of penile length, degree of the curvature and erectile function status should be done for all patients. If the degree of curvature is less than 60°, a penile shortening procedure is usually sufficient. If the degree of curvature is more than 60° or is a complex curvature, or if the penile length is short (with a good erectile function, with PDE5I or without), penile lengthening procedure is appropriate. However, if there is ED refractory to medical treatment, penile prosthesis implantation is preferred. The latter may be combined with an adjunct procedure in severe cases.

3.3. Potentials for the future − stem cell therapy

Regenerative urology represents a novel method with potential benefits in the treatment of different urological conditions including PD, with the use mesenchymal stem cell therapy [91]. The external location of the penis makes administration of local therapy, as stem cell therapy, technically feasible and easy. Moreover, mesenchymal pluripotent stem cells are readily available, and their use avoids the ethical issues associated with the use of embryonic stem cells. Also, autologous cells may be used, avoiding the issue of antigenic incompatibility [92]. Adipose-derived stem-cell (ADSC) may be the most suitable among mesenchymal stem cells, as they are abundant, and easily accessible [92]. The exact mechanism of action for ADSCs remain unclear; stem cells may differentiate and replace the damaged tissue; increase the local production of cytokines and growth factors; decrease inflammation and oxidative stress; or modulate the extracellular matrix [93]. One interesting finding is that ADSCs seem to migrate to the site of injury, probably in response to cytokine signaling [94].

In rats treated with intratunical injections TGF-β1, an established model for PD, ADSCs inhibited the development of PD. It decreased disordered collagen type III and elastin tissues (common in PD plaques) [95], which could be the basis for future research for their use in the treatment of PD in humans and the hope of interrupting the disease pathogenesis before it actually manifests.

4. Conclusion

PD is a common condition, whose exact etiology is still unknown. Prevalence is higher among patients with diabetes and ED. The disease has an acute phase and a chronic fibrotic phase. Early intervention is recommended

to improve outcomes. Non-surgical treatments are indicated for the acute phase to alleviate pain and stabilize the curvature and deformity, among which intralesional injection of clostridial collagenase seem the most effective. Surgical treatment is considered for stabilized disease for patients with severe deformities hindering sexual intercourse, or cases with ED refractory to medical treatment. Further research is needed to modulate the different fibrotic agents and enhance stem cell therapy for PD.

Conflicts of interest

The authors declare no conflict of interest.

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