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A clinical pathway for the management of Peyronie's disease: integrating clinical guidelines from the International Society of Sexual Medicine, American Urological Association and European Urological Association

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Objective

To provide a clinical framework and key guideline statements to assist clinicians in the evidence-based management of Peyronie's disease (PD).

Methods

We conducted a review of the published literature relevant to PD management, with an emphasis on published clinical guidelines. References used in the text have been assessed according to their level of evidence, and guideline recommendations have been graded based on the Oxford Centre for Evidence-based Medicine Levels of Evidence.

Results

The management of PD involves taking a detailed penile and sexual history, with a focused penile examination to identify plaque and hourglass deformity, and digital photographs of the erect curved (deformed) penis. Penile colour Duplex ultrasonography evaluates tunical plaque and underlying cavernosal smooth muscle and blood flow variables. The current therapy for PD can be divided into two main groups, namely, medical therapy and penile reconstructive surgery, and the patient should be counselled on the benefits and risks of each treatment option.

Conclusions

Peyronie's disease remains a clinical challenge and presents a considerable therapeutic dilemma as the current therapy addresses existing penile curvature only and is not very effective in preventing future penile fibrosis and/or reversing underlying erectile dysfunction.

Keywords

Peyronie's disease, clinical guideline, penile disorder, treatment outcomes, penile surgery

Key Messages

- Peyronie's disease (PD) is a psychosexual condition characterized by the presence of penile pain, curvature and/or deformity, with a potential palpable plaque and concomitant sexual dysfunction.
- Peyronie's disease is largely a progressive disorder, with approximately half of affected men reporting disease progression if left untreated.
- Penile colour Duplex ultrasonography remains the imaging method of choice and provides useful information on the tunical plaque, underlying cavernosal smooth muscle and blood flow variables.
- The current therapy for PD can be divided into two groups: medical therapy and penile reconstructive surgery, and the patient should be counselled on the benefits and risks of each treatment.
- Penile reconstructive surgery provides the fastest, most reliable and sustained outcomes for correction of penile deformity for stable PD. It is important to provide adequate preoperative counselling to set patients' expectations as surgery is often associated with risks of penile length loss, persistent or recurrent curvature, altered penile sensation and erectile dysfunction.

Introduction

Peyronie's disease (PD) is a relatively common psychosexual condition characterized by the presence of penile pain, curvature and/or deformity, palpable plaque(s) and erectile dysfunction (ED) [1]. The published literature shows a strong

association between PD and psychological issues such as depression, low self-esteem and altered relationship dynamics, with adverse impact on masculinity, sexual confidence and satisfaction [1–3].

Large population epidemiological studies report a discordance between the physician's and patient-reported perceptions; the rates of PD vary among different countries and across various institutions, highlighting that these differences may be related to different social views on self-reporting, the varying methodology used for clinical detection, as well as the diversity of sexual practices and perceived sexual dysfunction among men with PD. A recent national study conducted through a third party in Australia showed that at least one in 10 men reported a bend or curve in the penis [3]. Furthermore, the incidence of PD appears to be higher in men with cardiovascular and metabolic conditions such as diabetes and hypogonadism [4], while the presence of fibrotic disorders such as Dupuytren's contracture is more common in men with PD, especially among the older population [5].

While (repetitive) trauma to the erect penis is thought to be a causative factor for penile plaque formation [6,7], it is likely that the true pathophysiology for PD is multifactorial in nature [1]. Following an injury to the erect penis, there is a localized disruption of the tunica albuginea with the release of various cytokines and growth factors (predominantly TGFβ-1) as well as the proliferation of macrophages and fibroblasts resulting in excessive fibrin and collagen deposition [8]. Over time, the extracellular matrix becomes disorganized and cellular contraction ensues, with the de-differentiation of fibroblasts into myofibroblasts playing a pivotal role in the formation of fibrous plaque within the bilaminar tunical layers [9]. The presence of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases further contribute to plaque remodelling and penile deformity [10].

The natural history of PD remains controversial and spontaneous resolution of the penile plaque and curvature can occur in a minority of cases (probably <10%). PD is largely a progressive disorder with approximately half of affected men reporting disease progression if left untreated [11]. The PD process is traditionally divided into two main stages: an acute (inflammatory) phase in which the patient usually describes short-duration (<6 months), penile pain, or changing penile curvature and/or deformity [5], and a chronic (stable) phase which is characterized by an absence of pain, and the presence of penile plaque, complex deformity such as hinge or hourglass deformity, and erectile dysfunction. Recent clinical findings concerning the pathophysiology of PD, however, suggest this fibrotic process is a continuum and it is often difficult to predict whether the penile deformity will stabilize or progress further.

There is a great variation in clinical practice patterns in PD management and, despite published clinical guidelines, proposed treatment pathways are predominantly dictated by physician knowledge and past experiences [1]. The increasing volume of clinical studies on various effective therapeutic options for PD should enable clinicians to educate and counsel patients on evidence-based PD practice (Fig. 1) [1]. The present paper provides a framework based on current evidence recommendations from published clinical guidelines to assist clinicians and with which to develop personalized treatment plans with realistic expectations and treatment goals in the management of men with PD.

Methods

A literature search was conducted to identify published literature relevant to PD. Literature searches were performed on English-language publications using the Medline database with specific emphasis on published clinical guidelines from the International Consultation on Sexual Medicine/ International Society of Sexual Medicine [1], the AUA [12] and the European Association of Urology [13]. References used in the text have been assessed according to their level of evidence, and guideline recommendations have been graded based on the Oxford Centre for Evidence-based Medicine Levels of Evidence, and where there is insufficient high-quality evidence, recommendation statements are provided as clinical principles and/or expert opinion.

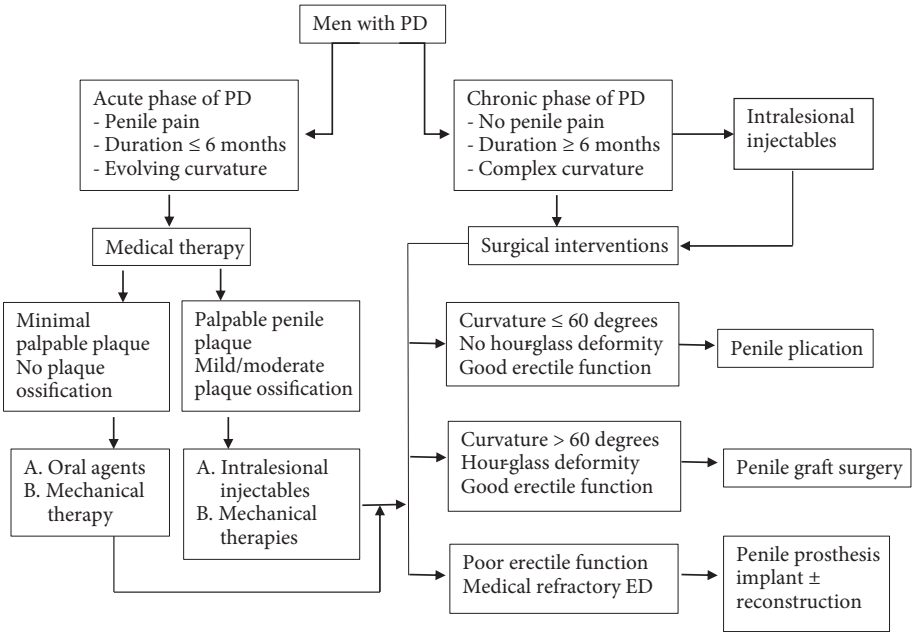
Results and Discussion

Patient Evaluation and Diagnosis: Clinical Principle/ Expert Opinion

The diagnosis of PD is usually apparent from a comprehensive clinical history and focused penile examination. Pertinent aspects to consider include: the status of disease (acute or chronic); the nature of curvature/deformity, its duration and change over time; preceding penile trauma; previous therapy; and associated medical comorbidities that may affect treatment options and outcomes [1,12,13]. It is important to distinguish between PD and congenital penile curvature, a condition that relates to uneven growth between the cavernosal bodies. In congenital penile curvature, the patient has a history of lifelong penile curvature without a hinge or complex deformity and there is no underlying palpable penile induration or plaque.

Assessment of sexual function should be carried out with emphasis on penile sensation, erectile and ejaculatory function, as well as concerns regarding penile length and girth. Patient and partner comfort and psychosocial distress should be documented. While a validated questionnaire such as the PD Questionnaire has been used in research, it is not widely adopted in clinical practice [14].

Fig. 1 Proposed treatment algorithm in PD. ED, erectile dysfunction; PD, Peyronie's disease



Clinical examination should provide baseline information on the presence of deformity, the point of maximum curvature, presence/location/size of the plaque, penile length, and areas of tenderness. On examination, the penis should be stretched fully to assess the penile length and palpate for the presence of any penile plaque [15,16]. Digital photographs are often helpful and penile examination with the aid of vasoactive intracavernosal injection can be used to confirm and document the extent of penile curvature/deformity, vascular integrity and erectile response [16].

Penile colour Duplex ultrasonography (CDU), with concurrent use of vasoactive injection, remains the diagnostic method of choice as it is safe, is low-cost and can objectively characterize PD [17]. Penile CDU features include a description of tunical thickening and/or calcification, intracavernosal or septal fibrosis and/or calcification, and mixed features [4]. Some PD ultrasound features correlate strongly with various clinical symptoms such as the presence of septal fibrosis and penile length loss, while tunical thickening and intracavernosal fibrosis were associated with veno-occlusive dysfunction, and a larger plaque size and impaired cavernosal arterial flow correlate strongly with ED [16]. Extensive plaque calcification probably signifies chronic disease which, in general, does not tend to respond to medical therapy [18]. In addition, penile CDU can provide useful information on the underlying penile vascular blood flow variables and possible cause of ED, be it arterial insufficiency or veno-occlusive dysfunction [19]. Other imaging methods, such as plain X-ray, CT and MRI, have not been shown to be superior to penile CDU and therefore are not recommended as routine investigations for PD.

Management of Peyronie's Disease

Despite published recommendations and various society guidelines [1,12,13], there is a lack of consensus among clinicians on the optimal and best practice in PD management. It is important to acknowledge that PD is probably a symptom complex with varying degrees of adverse effects on sexual function and psychosocial domains, therefore, it is important to have an open discussion with patients about the potential benefits of treatment against the treatment's risks.

Medical Therapy

Oral therapy (grade B, level 2) The clinical efficacy of oral therapy in PD remains questionable, and the published literature showed minimal benefit with respect to any significant decrease in penile deformity, which is probably attributable to the heterogeneity of these studies, which had small numbers of patients, different PD phases and limited objective outcome measures [1,12]. While randomized studies have shown that oral vitamin E, colchicine, carnitine, potassium aminobenzoate and tamoxifen are largely ineffective [20], recent studies highlighted a potential positive role for pentoxifylline [21] and low-dose tadalafil [22] in PD. Oral medical therapy may play an important role in the early phase of PD, especially in men with unstable or progressive penile curvature and painful erection, as well as those not psychological ready or interested in surgical intervention (Fig. 1).

Intralesional therapy (grade B, level 2) Intralesional injections are suitable in men with stable disease, i.e. small clinical palpable, non-ossified plaque disease and mild/moderate penile curvature [1,12]. Of the injectable agents in PD, verapamil, interferon-α2B and collagenase *Clostridium histolyticum* (CCH) are shown to be effective in placebo-controlled trials [23]. To date, CCH remains the only drug licensed for the treatment of PD, and penile manual remodelling is an important adjunctive manoeuvre in patients who received intralesional therapy. Safety data show that intralesional CCH is generally well tolerated and common adverse events reported include penile haematomas, pain and swelling, while serious complications such as severe penile haematomas and corporal rupture are rare [23]. Previous intralesional CCH therapy should not adversely affect subsequent surgical intervention.

Mechanical therapy (grade B, level 3) Published studies on the efficacy of low-intensity extracorporeal shockwave therapy on PD-related deformity have not had robust results. The current literature suggests that low-intensity extracorporeal shockwave therapy appears to be effective in reducing penile pain, and at best, has a potential beneficial effect on disease stabilization but does not lead to significant improvement in plaque size and penile curvature [1,12]. Nonetheless, these outcomes should be interpreted with some caution due to underlying methodological flaws and perhaps inappropriate use of shockwave energy flow density [24,25]. Subgroup analysis of patients in the low-intensity extracorporeal shockwave therapy group showed overall better outcomes in younger patients with a relatively mild degree of curvature [26].

Evidence for iontophoresis or transdermal electromotive administration of drugs, such as dexamethasone, or verapamil, remains equivocal and further studies are required to fully evaluate their role in PD [1,12]. It is possible that the observed reduction in curvature reflects the energy delivered to the tunica rather than the actual effect of the drug. Iontophoresis appears to be clinically safe, with transient skin erythema reported from the dispersive electrodes.

Penile traction therapy is effective in increasing penile length and reducing the penile deformity as well as possibly penile pain [27]. The ideal candidates for penile traction therapy are patients in the acute phase of PD with a short penis, and who have large penile curvature with no calcified penile plaque or complex penile deformity and normal erectile function. Patients also need to be highly motivated and compliant with a traction device used for a minimum of 4–6 h per day for a minimum of 3–6 months in order to gain maximal benefit.

Penile Reconstructive Surgery (Grade B, Level 3)

Penile reconstructive surgery provides the fastest, most reliable and sustained outcomes for correction of penile deformity in men with stable PD (at least 6–12 months after the onset of PD or once the deformity has remained stable and painless for at least 3 months) and following failure of conservative treatment. Men who want the quickest and most reliable outcome should consider surgery [1,12,13]. The severity of penile deformity and underlying erectile function are two key preoperative factors that determine the choice and success of the surgery. The erectile function should be assessed preoperatively to determine if penile prosthesis implantation is preferred over reconstructive surgery alone. Other factors to consider include the direction and severity of the penile curvature, existing penile length, the presence of a destabilizing hinge effect caused by severe indentation or hourglass deformity, and the patient's expectations regarding the outcomes of surgical intervention [28].

Psychosexual stressors are common in men with PD, who sometimes have unattainable expectations regarding the outcome from surgical reconstruction [29]. It is important to provide adequate preoperative counselling to set patients' expectations as surgery is often associated with risks of penile length loss, persistent or recurrent curvature, ED, and altered penile sensation [1,12,13]. No surgical procedure has been proven to be superior to its counterpart in terms of clinical outcomes, but plication surgery is effective and can be performed with low risk of *de novo* ED and sensory loss, while graft reconstruction allows restoration of penile size [30].

Penile plication (Grade B, Level 3) Modified penile plication procedures, such as the Nesbitt procedure, the Yachia technique and Lue's 16-dot procedure, are designed to shorten the longer side of the penis to compensate for the contralateral curvature. The traditional Nesbitt procedure with excision of an ellipse of tunica can increase the risk of ED secondary to postoperative veno-occlusive dysfunction [28]. It is estimated that men lose ~1 cm of penile length with each 30° penile curvature correction [1,12]. In summary, the major advantages of plication procedures are that they are simple, minimally invasive and tend to preserve potency in patients (estimated risk of postoperative ED is <5%) [1,12,13]. The disadvantages are that plication procedures invariably result in penile length loss and that they do not address and may in fact, worsen an existing hourglass or hinge effect, particularly if larger plications are used.

Penile graft surgery (Grade B, Level 3) Penile lengthening surgery with graft reconstruction is ideal for patients with a normal penile erection strength, but who report severe penile length loss and curvature and/or prominent hourglass deformity. The graft is applied to the defect following incision of the most prominent point of the concave penis where the plaque resides and thus penile lengthening is achieved. Plaque incision or partial excision is the preferred technique over

plaque excision to minimize disruption of the underlying veno-occlusive mechanism [31]. While immediate postoperative length loss is minimal, long-term follow-up studies showed greater risks such as ED (up to 60%), length loss (~20%) and recurrence of curvature (20%) [1,32,33]. While the ideal graft material remains elusive, various autologous tissues such as dermis, vein or Tunical tissue, and allograft and xenograft materials such as pericardium, small intestinal submucosal and dermis, have been used with reasonable outcomes [32]. The choice of graft material is often determined by the surgeon's experience and the availability of graft material. Postoperative penile rehabilitation is advisable and often involves the use of oral phosphodiesterase type 5 inhibitors and/or penile traction therapy [1]. Complex penile reconstruction is a highly technical and demanding surgery and should be performed by surgeons with extensive prosthetic and reconstructive experience since the risk of sensory loss, glans ischaemia/necrosis, ED and failure to gain any meaningful length are serious postoperative concerns that can be difficult to treat [33].

Penile prosthesis implant ± penile reconstruction (Grade B, Level 3) For men who have ED and wish to preserve their penile size, penile prosthesis implantation is recommended [34]. The inflatable penile prosthesis implant offers higher functional and patient satisfaction rates, compared to malleable implants [1,12]. Comparative studies have shown no statistically significant difference in terms of clinical outcomes and patient satisfaction rates between the Boston Scientific AMS 700 series and Coloplast Titan IPPI [35].

While the implantation of penile prosthesis alone is often sufficient to straighten small penile curvature, those with residual curvature >30° may need repeated manual modelling or other adjunctive manoeuvres, such as penile plication and/or plaque incision with grafting, at the time of surgery [1,12,13]. The use of graft material is associated with a higher risk of prosthetic infection [1]. Novel surgical techniques to improve penile lengthening and girth at the time of penile prosthesis implantation using various modified sliding techniques [33] have been reported with high patient satisfaction rates and relatively small but serious complications such as glans necrosis and penile gangrene [36].

In conclusion, despite significant advances over the last decade, there is a need for greater understanding of the molecular basis and search for more innovative treatment options in PD. To date, PD continues to pose a clinical challenge and therapeutic dilemma. Further collaborative clinical trials will need to be conducted with stricter methodology and meaningful objective outcome measures and be replicated and validated across multiple institutions and countries.

While the existing therapy addresses the penile curvature, it is not very effective in preventing future penile curvature. Hopefully, the increased knowledge and utility of translational research with the use of regenerative technology will address penile fibrosis and ultimately restore the penile size and erectile function in men with PD in the near future.

Conflicts of Interest

None declared.

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Abbreviations: PD, Peyronie's disease; ED, erectile dysfunction; CDU, colour Duplex ultrasonography; CCH, collagenase *Clostridium histolyticum*.