Guidelines on

Penile Curvature

E. Wespes (chairman), K. Hatzimouratidis (vice-chair), I. Eardley,
F. Giuliano, D. Hatzichristou, I. Moncada, A. Salonia, Y. Vardi

European
Association
of Urology

TABLE OF CONTENTS PAGE

1. INTRODUCTION

Penile curvature can be congenital or acquired. Congenital curvature is discussed in these guidelines as a distinct pathology in the adult population without any other concomitant abnormality present (such as urethral abnormalities). For paediatric congenital penile curvature, please refer to the EAU Guidelines on Paediatric Urology, Chapter 7, Congenital Penile Curvature.

Acquired curvature is secondary due to La Peyronie's disease (referred as Peyronie's disease in this text), which was named by a French physician, François Gigot de La Peyronie, in 1743 – although he was not the first one to describe this disease (1).

2. METHODOLOGY

A systematic literature search of the Medline database was performed by panel members. The controlled vocabulary of the Medical Subject Headings (MeSH) database uses the specific term 'penile induration' for Peyronie's disease. There is no specific MeSH term for congenital penile curvature. In order to identify relevant articles, search included the MeSH terms 'congenital abnormalities', 'penis/*abnormalities' and 'male' as well as the free text term 'congenital penile curvature'. Since this is the first time guidelines on this topic are published, the search includes all relevant articles published up to January 2012. A total of 48 articles were identified for congenital penile curvature while this number was 1200 for Peyronie's disease. The panel reviewed all these records and selected the articles with the highest evidence available. However, in several subtopics only articles with low levels of evidence were available and discussed accordingly.

2.1 Level of evidence and grade of recommendation

The level of evidence (LE) and grade of recommendation (GR) provided in this guideline follow the listings in Tables 1 and 2. The aim of grading the recommendations is to provide transparency between the underlying evidence and the recommendation given.

Table 1: Level of evidence*

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

**Modified from Sackett et al. (2).*

It should be noted that when recommendations are graded, there is not an automatic relationship between the level of evidence and the grade of recommendation. The availability of RCTs may not necessarily translate into a grade A recommendation if there are methodological limitations or disparities in the published results. Conversely, an absence of high-level evidence does not necessarily preclude a grade A recommendation if there is overwhelming clinical experience and consensus. In addition, there may be exceptional situations in which corroborating studies cannot be performed, perhaps for ethical or other reasons. In this case, unequivocal recommendations are considered helpful for the reader. Whenever this occurs, it has been clearly indicated in the text with an asterisk as 'upgraded based on panel consensus'. The quality of the underlying scientific evidence is a very important factor, but it has to be balanced against benefits and burdens, values and preferences and costs when a grade is assigned (3–5).

The EAU Guidelines Office does not perform cost assessments, nor can they address local/national preferences in a systematic fashion. However, whenever such data are available, the expert panels will include the information.

Table 2: Grade of recommendation*

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

**Modified from Sackett et al. (2).*

2.2 Publication history

The present Penile Curvature guidelines are a new publication that underwent a blinded peer-review process before publication. The standard procedure will be an annual assessment of newly published literature in this field, guiding future updates. An ultra-short reference document is being published alongside this publication. All documents are available with free access through the EAU website Uroweb (http://www.uroweb.org/guidelines/online-guidelines/).

2.3 Potential conflict of interest statement

The expert panel have submitted potential conflict of interest statements which can be viewed on the EAU website: http://www.uroweb.org/guidelines/online-guidelines/.

3. CONGENITAL PENILE CURVATURE

3.1 Epidemiology and physiopathology

Congenital curvature is rare: one study reports an incidence of less than 1% (6) while another suggests it is more common with prevalence rates of 4-10% in the absence of hypospadias (7).

There is no evident cause of congenital penile curvature. A single study analysing the ultrastructure of the tunica albuginea has demonstrated widening and fragmentation of collagen fibres, with complete disappearance of striation and transformation into electron-dense, fibrous, granulated material and elastin accumulation (8).

3.2 Patient evaluation

Taking medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is only useful to document curvature and exclude other pathologies (9). Erectile function is normal but it can be compromised by excessive curvature.

3.3 Treatment

Only androgens have been tried for congenital penile curvature with no improvement in adults (10). Therefore, the treatment of this pathology is only surgical. Surgical treatments for congenital penile curvature generally share the same principles as in Peyronie's disease (presented in detail in the next section) but can be performed at any time in adults. Notably, most operations for Peyronie's disease have been described first for congenital penile curvature (11). Plication techniques are used almost exclusively with high curvature correction rates (67-97%) (12-14). The use of grafting material in isolated congenital penile curvature is very limited to draw any conclusions (15).

Conclusions on treatment	LE
Medical and sexual history are usually sufficient to establish the diagnosis of congenital penile curvature. Physical examination during erection is useful for documentation of the curvature and exclusion of other pathologies.	3
Surgery is the only treatment option which can be performed at any time in adult life. Plication techniques have been used almost exclusively in isolated penile curvature with high curvature correction rates.	3

4. PEYRONIE'S DISEASE

4.1 Epidemiology, physiopathology and natural history

Epidemiological data on Peyronie's disease are limited. Prevalence rates of 0.4-9% have been published (16-22).

The etiology of Peyronie's disease is unknown. However, an insult (repetitive microvascular injury or trauma) to the tunica albuginea is the most widely accepted hypothesis on the etiology of the disease (23). Peyronie's disease starts with an acute inflammatory process. The acute inflammation is characterised by increased proliferation of the tunical fibroblasts, some of which differentiate into myofibroblasts, with excessive deposition of collagen, persistence of fibrin and elastin fragmentation. A prolonged inflammatory response will result in the remodelling of connective tissue into a dense fibrotic plaque (23-25). Penile plaque formation can result in curvature which, if severe, may prevent vaginal intromission. The most commonly associated comorbidities and risk factors are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, erectile dysfunction, smoking, and excessive consumption of alcohol (21,22,26,27). Dupuytren's contracture is more common in patients with Peyronie's disease affecting 9-39% of patients (18,28-30) while 4% of patients with Dupuytren's contracture reported Peyronie's disease (28). However, it is still unclear if these factors contribute to the pathophysiology of Peyronie's disease. While the pathogenesis has to be clarified, younger men and Caucasian men are at increased risk for Peyronie's disease after radical pelvic surgery, e.g. radical prostatectomy (31).

Peyronie's disease can be a chronic and progressive disease. Two phases of the disease can be distinguished (32). The first is the acute inflammatory phase, which may be associated with pain in the flaccid state or painful erections and manifestation of a 'soft' nodule/plaque and penile curvature. The second is the fibrotic phase with the formation of hard palpable plaques that can be calcified, which also result in disease stabilisation. With time, penile curvature is expected to worsen in 30-50% of patients or stabilise in 47-67% of patients, while spontaneous improvement has been reported by only 3-13% of patients (27,33,34). An improvement in penile curvature is more likely to occur in the early stage of the disease, rather than in a later phase when the plaque has been formed and has become densely calcified (35). Pain is present in 35-45% of patients during the early stages of the disease (36). Pain tends to resolve with time in 90% of men, usually during the first 12 months after the onset of the disease (33,34).

In addition to physiological and functional alteration of the penis, affected men also suffer significant distress. Validated mental health questionnaires have shown that 48% of men with Peyronie's disease have mild or moderate depression, sufficient to warrant medical evaluation (37).

Conclusions	**LE**
Peyronie's disease is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity.	2
The contribution of associated comorbidities or risk factors (e.g. diabetes, hypertension, lipid abnormalities and Dupuytren's contracture) to the pathophysiology of Peyronie's disease is still unclear.	3
Two phases of the disease can be distinguished. The first phase is the acute inflammatory phase (painful erections, 'soft' nodule/plaque), and the second phase is the fibrotic/calcifying phase with formation of hard palpable plaques (disease stabilisation).	2
Spontaneous resolution is uncommon (3-13%) and most patients experience disease progression (30-50%) or stabilisation (47-67%). Pain is usually present during the early stages of the disease but tends to resolve with time in 90% of men.	2

4.2 Patient evaluation

The aim of the initial evaluation is to provide information on the presenting symptoms and their duration (erectile pain, palpable nodules, curvature, length, rigidity, and girth) and erectile function status. It is mandatory to obtain information on the distress provoked by the symptoms and the potential risk factors for erectile dysfunction and Peyronie's disease. Although a disease-specific questionnaire has been designed to collect data, it is yet a validated instrument suitable for use in clinical practice (38).

Major attention should be given to whether the disease is still active, as this will influence medical treatment or the timing of surgery. Patients who are still likely to have an active disease are those with short symptom

duration, pain during erection, or a recent change in penile curvature. It is often difficult to evaluate the end of the inflammatory phase, but resolution of pain and stability of the curvature for at least 3 months are well-accepted criteria of disease stabilisation and patients referral for surgical intervention when indicated (*see below* Section 4.4.4 Surgical treatment of penile curvature) (33).

The examination should start with a routine genitourinary assessment, which is then extended to the hands and feet for detecting possible Dupuytren's contracture or Ledderhose scarring of the plantar fascia (34). Penile examination consists generally of a palpable node or plaque. The whole of the penis should be examined. There is currently no standardised approach, but it is recommended to measure the penis dorsally from the base to the tip of the glans while at full stretch (34). Plaque size is measured in the erect penis. However, there is no correlation between plaque size and the degree of curvature (35). Measurement of length during erection is important because it impacts directly on treatment decisions (39). Girth-related changes are often self-reported by the patients.

Erectile function can be assessed using validated instruments such as the international index of erectile function (IIEF) (40). However, it should be noted that IIEF has not been validated specifically in Peyronie's disease patients. Erectile dysfunction is quite common (> 50%) in patients with Peyronie's disease but it is important to define if pre-dated or post-dated Peyronie's disease onset. It is mainly due to penile vascular disease (27,35). The presence of erectile dysfunction may impact on the treatment strategy (41).

Sonographic measurement of the plaque's size is inaccurate and operator dependent and it is not recommended in everyday clinical practice (42). Duplex ultrasonography may be required for the assessment of vascular parameters (41) (see also Section 2.5.3.3 and Table 3 in the EAU Guidelines on Male Sexual Dysfunction). An objective assessment of penile curvature with an erection is mandatory. This can be obtained by a home (self) photograph of a natural erection (preferably) or using a vacuum-assisted erection test or an intracavernosal injection using vasoactive agents (38).

Guidelines recommendations on the evaluation of Peyronie's disease	**LE**	**GR**
Medical and sexual history in patients with Peyronie's disease must include duration of the disease, penile pain, change of penile deformity, difficulty in vaginal intromission due to deformity, and erectile dysfunction.	2	B
Physical examination must include assessment of palpable nodules, penile length, extent of curvature (self-photograph, vacuum-assisted erection test or pharmacological-induced erection) and any other possibly related diseases (Dupuytren's contracture, Ledderhose disease).	2	B
Sonographic measurement of the plaque's size is inaccurate and operator dependent. It is not recommended in everyday clinical practice.	3	C
Duplex ultrasonography is required to ascertain vascular parameters associated to erectile dysfunction.	2	B

4.3 Non-operative treatment

Conservative treatment of Peyronie's disease is primarily focused on patients in the early stage of disease, when symptoms are present and the plaque is not densely fibrotic or calcified (34,43). In this context, several options have been suggested, including oral pharmacotherapy, intralesional injection therapy and other topical treatments, which will be discussed in this section (Table 1). The role of conservative treatment in men with stable/chronic disease has not yet been adequately defined (32,44). No single drug has been approved by the European Medical Association for the treatment of Peyronie's disease. Only potassium para-aminobenzoate (Potaba) has been classified as 'possibly effective' by the Food and Drug Administration for the treatment of Peyronie's disease.

The results of the studies on conservative treatment for Peyronie's disease are often contradictory making it difficult to provide recommendations in the everyday, real-life setting. This fact is due to several methodological problems including uncontrolled studies, limited number of patients treated, short term follow-up and different outcome measures (44). Moreover, the efficacy of conservative treatment in distinct patient population in terms of early (inflammatory) or late (fibrotic) phases of the disease is not yet available.

Table 1: Non-operative treatments for Peyronie's disease

Oral treatments
Vitamin E
Potassium para-aminobenzoate (Potaba)
Tamoxifen
Colchicine
Acetyl esters of carnitine
Pentoxifylline
Intralesional treatments
Steroids
Verapamil
Clostridial collagenase
Interferon
Topical treatments
Verapamil
Iontophoresis
Extracorporeal shock wave lithotripsy (SWL)
Traction devices
Vacuum devices

*4.3.1 **Oral treatment***

4.3.1.1 Vitamin E

Vitamin E (tocopherol, a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in energy metabolism) is commonly prescribed by the majority of urologists at once or twice daily doses of 400 IU because of its wide availability, low cost and safety (45). Despite the fact that it has been suggested as a potential treatment option in patients with Peyronie's disease (46), a double-blind, placebo-controlled crossover study failed to show a significant effect on penile deformity or plaque size (47).

4.3.1.2 Potassium para-aminobenzoate (Potaba)

Potassium para-aminobenzoate is thought to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and an enhancement of the activity of monoamine oxidases (48). Its role in the treatment of Peyronie's disease is due to preliminary studies that reported an improvement in penile curvature, penile plaque size, and penile pain during erection (49). In a prospective double-blinded controlled study in 41 patients with Peyronie's disease, potassium paraaminobenzoate (12 g/day for 12 months) improved penile pain significantly, but not penile curvature and penile plaque size (50). In another prospective, randomised, double-blind, placebo-controlled in 103 patients with Peyronie's disease, potassium para-aminobenzoate (4 x 3g/day for 12 months) decreased penile plaque size significantly, but had no effect on penile curvature or penile pain (51). However, the pre-existing curvature under potassium para-aminobenzoate remained stable, suggesting a protective effect on the deterioration of penile curvature. Treatment-emergent adverse events are nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion and difficulty in concentration, but no serious adverse events were reported.

4.3.1.3 Tamoxifen

Tamoxifen is a non-steroidal oestrogen receptor antagonist. Its proposed mechanism of action in Peyronie's disease involves the modulation of TGFβ1 secretion by fibroblasts. Preliminary studies reported that tamoxifen (20 mg twice daily for 3 months) improved penile pain, penile curvature, and reduced the size of penile plaque (52). However, a placebo-controlled, randomised study (in only 25 patients, at late stage of the disease with a mean duration of 20 months) using the same treatment protocol, failed to show any significant improvement in pain, curvature, or plaque size in patients with Peyronie's disease (53).

4.3.1.4 Colchicine

Colchicine is a medicine often used to treat acute attacks of gout. It has been introduced into the treatment

of Peyronie's disease on the basis of its anti-inflammatory effect (54). Preliminary results in 24 men showed that half of the men given colchicine (0.6-1.2 mg daily for 3-5 months) found that painful erections and penile curvature improved, while penile plaque decreased or disappeared in 50% (55). In another study in 60 men (colchicine 0.5-1 mg daily for 3-5 months with escalation to 2 mg twice daily), penile pain resolved in 95% and penile curvature improved in 30% (54). Similar results have been reported in another uncontrolled retrospective study in 118 patients. The study concluded that lateral curvature is the most commonly altered deformity, which mostly shifts to the dorsal size of the penis after colchicine therapy (56). Reported treatment-emergent adverse events with colchicine are gastrointestinal effects (nausea, vomiting, diarrhoea) that can be improved with dose escalation (54).

The combination of vitamin E and colchicine (600 mg/day and 1 mg every 12 hours, respectively) for 6 months in patients with early-stage Peyronie's disease resulted in significant improvement in plaque size and curvature, but not in pain compared to ibuprofen 400 mg/day for 6 months (57).

4.3.1.5 Acetyl esters of carnitine

Although the actual mechanism of action of acetyl esters of carnitine in patients with Peyronie's disease is unknown, it has been suggested that it can reduce intracellular calcium levels in endothelial cells (58). This may eventually suppress fibroblast proliferation and collagen production, thus reducing penile fibrosis. In a randomised, double-blind study in 48 patients with early-stage Peyronie's disease, patients were randomised to acetyl-L-carnitine (1 g twice daily) compared to tamoxifen (20 mg twice daily). After 3 months, acetyl-L-carnitine was significantly more effective than tamoxifen in pain and curvature reduction and in inhibiting disease progression but not in penile plaque size reduction (both drugs significantly reduced plaque size) (59). Tamoxifen induced significantly more side-effects.

Finally, the combination of intralesional verapamil (10 mg weekly for 10 weeks) with propionyl-l-carnitine (2 g/day for 3 months) significantly reduced penile curvature, plaque size, and disease progression compared to intralesional verapamil combined with tamoxifen (40 mg/day) for 3 months (60).

4.3.1.6 Pentoxifylline

Pentoxifylline is a non-specific phosphodiesterase inhibitor which down regulates TGFβ1 and increases fibrinolytic activity (61). Moreover, an increase of nitric oxide levels may be effective in preventing progression of Peyronie's disease or reversing fibrosis (62). Preliminary data from a case report showing that pentoxifylline (400 mg three times daily for 6 months) improved penile curvature and the ultrasonographic appearance of the plaque (62). In another study in 62 patients with Peyronie's disease, pentoxifylline treatment for 6 months appeared to stabilise or reduce calcium content in penile plaques (63).

4.3.1.7 Phosphodiesterase type 5 inhibitors (PDE5i)

The rationale for the use of PDE5i in Peyronie's disease comes from animal studies showing that they can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in the Peyronie's disease-like plaque (64). In a retrospective controlled study, daily tadalafil (2.5mg for 6 months) resulted in statistically significant ($p < 0.05$) resolution of septal scar in 69% of patients compared to 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity (65). Therefore, no recommendation can be given for PDEi in patients with Peyronie's disease.

4.3.2 ***Intralesional treatment***

Injection of pharmacologically active agents directly into penile plaques represents another treatment option. It allows a localised delivery of a particular agent that provides higher concentrations of the drug inside the plaque. However, delivery of the compound to the target area is difficult to ensure.

4.3.2.1 Steroids

Intralesional steroids are thought to act by opposing the inflammatory milieu responsible for Peyronie's plaque progression via inhibition of phospholipase A2 and suppression of the immune response and by decreasing collagen synthesis (66). In small, non-randomised studies, a decrease in penile plaque size and pain resolution was reported (67,68). In the only single-blind, placebo-controlled study with intralesional administration of betamethasone, no statistical significant changes in penile deformity, penile plaque size, and penile pain during erection were reported (69). Adverse effects include tissue atrophy, thinning of the skin and immune suppression (67).

4.3.2.2 Verapamil

The rationale for intralesional use of verapamil (a calcium channel antagonist) in patients with Peyronie's disease is based on in-vitro data that demonstrated transport of extracellular matrix molecules, which included

collagen, fibronectin, and glycosaminoglycans as a calcium-dependent process, along with a concomitant increase in collagenase activity, a modification of the inflammatory response in the early phase of the disorder, and the inhibition of fibroblast proliferation in the plaques (70,71). A number of studies have reported that intralesional verapamil injection may induce a significant reduction in penile curvature and plaque volume (72-76). These findings suggested that intralesional verapamil injections (multiple-puncture technique, 10 mg of verapamil diluted to 10 mL, distributed throughout the plaque every 2 weeks for a total of 12 consecutive sessions) could be advocated for the treatment of non-calcified acute phase or chronic plaques to stabilise disease progression or possibly reduce penile deformity, although large scale, placebo-controlled trials have not yet been conducted (72). Side effects are uncommon (4%) and minor including nausea, light-headedness, penile pain, and ecchymosis (72). However, in the only randomised, placebo-controlled study, no statistical significant differences on plaque size, penile curvature, penile pain during erection and plaque 'softening' were reported (77). Younger age and larger baseline penile curvature were found to be predictive of favourable curvature outcomes in a case-series study (78).

4.3.2.3 Clostridial collagenase

Clostridial collagenase is a chromatographically purified bacterial enzyme that selectively attacks collagen, which is known to be the primary component of the Peyronie's disease plaque (79-81). Conversely, clostridial collagenase injections received FDA approval for Dupuytren's contracture, with a similar mechanism of action (82). In a prospective randomised, placebo-controlled, double-blind study, comparing the effects on plaque size and penile deformity of intralesional purified clostridial collagenase (6,000-14,000 units) and saline placebo, the overall response was 36% while in the placebo arm it was 4% ($p < 0.007$) (79). Follow-up was only 3 months. The response rates were even higher in patients with smaller plaques and curvature less than 60º. The efficacy of intralesional collagenase injections (three injections of clostridial collagenase 10,000 unit/0.25 cm3 per injection administered over 7-10 days and subsequently administered over 7-10 days at 3 months) has been assessed over a non-placebo-controlled, short-term follow-up study conducted in a small population of men with Peyronie's disease (81). Although methodologically-biased, this study showed significant decreases from baseline in the deviation angle, in plaque width and in plaque length. The most commonly reported side effects were penile pain, contusions, and ecchymosis.

4.3.2.4 Interferon

Interferon α-2b has been shown to decrease fibroblast proliferation, extracellular matrix production and collagen production from fibroblasts and improved the wound healing process from Peyronie's disease plaques in vitro (83). Intralesional injections (5×10^6 units of interferon α-2b in 10 mL saline, two times per week for 12 weeks) significantly improved penile curvature, plaque size and density, and pain compared to placebo (84,85). Side effects include myalgias, arthralgia, sinusitis, fever and flu-like symptoms. They can be effectively treated with non-steroidal anti-inflammatory drugs before interferon injection.

4.3.3 ***Topical treatments***

4.3.3.1 Topical verapamil

In a small, randomised, placebo-controlled study, topical verapamil (gel 15% applied topically to the penile shaft twice daily) significantly improved penile curvature, plaque size, and penile pain (86). Moreover, treatment results significantly improved after 9 months compared to 3 months showing that a prolonged treatment period may be important. However, there is lack of evidence that topical verapamil applied to the penile shaft results in adequate levels of the active compound within the tunica albuginea (87).

4.3.3.2 Iontophoresis

Iontophoresis (also known as transdermal electromotive drug administration or electromotive drug administration [EMDA]) has been introduced to try and overcome limitations on the local uptake of the drugs themselves. Uncontrolled studies showed promising results in terms of improvement in penile curvature, plaque size and penile pain during erection (88-90).

In a randomised, double-blind, controlled study, iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in a statistically significant improvement in penile curvature and plaque size (91). However, in another randomised, double-blind, placebo-controlled study, penile curvature was not statistically improved after iontophoresis with verapamil 10 mg (92). The method is not associated with any significant adverse event.

4.3.3.3 Extracorporeal shock wave lithotripsy (SWL)

The mechanism of action involved in SWL for Peyronie's disease is still unclear, but there are two hypotheses. In the first hypothesis, shock wave therapy works by directly damaging and remodelling the penile plaque. In the second hypothesis, SWL increases the vascularity of the area by generating heat resulting in an inflammatory reaction, with increased macrophage activity causing plaque lysis and eventually leading to

plaque resorption (93). Most uncontrolled studies failed to show significant improvements in patients with Peyronie's disease (94-96). In a prospective, randomised, double-blind, placebo-controlled study, four weekly treatment sessions of SWL, with each session consisting of 2000 focused shock waves, resulted in significant improvement only for penile pain (97).

4.3.3.4 Traction devices

The application of continuous traction in Dupuytren's contracture increases the activity of degradative enzymes (98). This initially leads to a loss of tensile strength and ultimately to solubilisation. It is followed by an increase in newly synthesised collagen (98). This concept has been applied in an uncontrolled study, including 10 patients with Peyronie's disease (the FastSize Penile Extender was applied as the only treatment for 2-8 hours/day for 6 months) (99). Penile curvature reduced in all men from 10° to 45°, with an average reduction of 33% (range: 51-34°). The stretched penile length increased to 0.5-2.0 cm. The erect girth increased to 0.5-1.0 cm, with a correction of hinge effect in four out of four men. There were no adverse events, including skin changes, ulcerations, hypoesthesia or diminished rigidity.

However, in another uncontrolled study in 15 patients with Peyronie's disease and a curvature of less than 50° (the Andropenis penile extender was applied for at least 5 hours per day for 6 months). The decrease in penile curvature was minimal (4°, the effect size was not reached), while the mean stretched and flaccid penile length increased by 1.3 and 0.83 cm, respectively, at 6 months (100).

4.3.3.5 Vacuum devices

The application of vacuum devices follows the same principles as traction devices. Their efficacy has been assessed in an uncontrolled study (31 patients completed the study) (101). They used a vacuum device for 10 min twice daily over a 12 week period. Penile pain reduced significantly ($p = 0.012$). Stretched penile length also increased significantly ($p = 0.029$) with a mean of 0.5 cm. Reduction of the curvature was reported in 67% of patients while 10% of them had a worsening and 23% had no change. Half of them were satisfied with outcome and the remaining had their curvature corrected surgically.

Guidelines recommendations on non-operative treatment for Peyronie's disease	**LE**	**GR**
Conservative treatment for Peyronie's disease is primarily aimed at treating patients in the early stage of disease. It is an option in patients not fit for surgery or when surgery is not acceptable to the patient.	3	C
Oral treatment with potassium para-aminobenzoate may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilisation.	1b	B
Intralesional treatment with verapamil may induce a significant reduction in penile curvature and plaque volume.	1b	C
Intralesional treatment with clostridial collagenase showed significant decreases in the deviation angle, plaque width and plaque length.	2b	C
Intralesional treatment with interferon may improve penile curvature, plaque size and density, and pain.	1b	B
Topical verapamil gel 15% may improve penile curvature and plaque size.	1b	B
Iontophoresis with verapamil 5 mg and dexamethasone 8 mg may improve penile curvature and plaque size.	1b	B
Extracorporeal shock-wave treatment fails to improve penile curvature and plaque size, and should not be used with this intent but may be beneficial for penile pain.	1b	B
Penile traction devices and vacuum devices may reduce penile deformity and increase penile length.	3	C
Recommendations AGAINST		
Intralesional treatment with steroids is not associated with significant reduction in penile curvature, plaque size or penile pain. Therefore intralesional treatment with steroids cannot be recommended.	1b	B
Oral treatment with vitamin E and tamoxifen are not associated with significant reduction in penile curvature, plaque size or penile pain thus should not be used with this intent.	2b	B
Other oral treatments (acetyl esters of carnitine, pentoxifylline) are not recommended.	3	C

4.4 Surgical treatment

Although conservative treatment for Peyronie's disease should resolve painful erections in most men, only a small percentage will experience any significant straightening of the penis. The aim of surgery is to correct curvature and allow satisfactory intercourse (102). Surgery is indicated only in patients with stable disease for at least 3 months, although a 6-12 month period has also been suggested (103).

During informed consent, the potential aims and risks of surgery should be discussed. Specific issues that should be mentioned during consent are the risks of penile shortening, erectile dysfunction, penile numbness, the risk of recurrent curvature, the potential for palpation of knots and stitches underneath the skin, and the potential need for circumcision at the time of surgery (32).

Two major types of repair may be considered for both congenital penile curvature and Peyronie's disease: penile shortening and penile lengthening procedures (104). Penile shortening procedures include the Nesbit wedge resection and the plication techniques performed on the convex side of the penis. Penile lengthening procedures are performed on the concave side of the penis and require the use of a graft. They aim to minimise penile shortening caused by Nesbit or plication of the tunica albuginea or correct complex deformities. Penile degloving with associated circumcision (as a means of preventing post-operative phimosis) is considered the standard approach for all types of procedures (104). However, recent data suggests that circumcision is not always necessary. In cases where the foreskin is normal pre-operatively, circumcision is unnecessary (105). Finally, in patients with Peyronie's disease and erectile dysfunction not responding to medical treatments, the surgical correction of the curvature with concomitant penile prosthesis implantation should be considered (106).

Choosing the most appropriate surgical intervention is based on penile length assessment, curvature severity and on the erectile function status, including response to pharmacotherapy in cases of erectile dysfunction (32). Patient expectations from surgery must also be included in the pre-operative assessment. There are no standardised questionnaires for the evaluation of surgical outcomes (102). Data from well-designed prospective studies are scarce, with a low level of evidence. Most data are mainly based on retrospective studies, typically non-comparative and non-randomised, or on expert opinion (32,107).

*4.4.1 **Penile shortening procedures***

In 1965, Nesbit was the first to describe the removal of tunical ellipses opposite a non-elastic corporal segment to treat congenital penile curvature (11). Fourteen years later, this technique became a successful treatment option, also for Peyronie's disease (108). This operation is based on a 5-10 mm transverse elliptical excision of the tunica albuginea or approximately 1 mm for each 10º of curvature (104). The overall short- and long-term results of the Nesbit operation are excellent. Complete penile straightening is achieved in more than 80% of patients (109). Recurrence of the curvature and penile hypoesthesia are uncommon (about 10%) and the risk of post-operative erectile dysfunction is minimal (104,110). Penile shortening is the most commonly reported outcome of the Nesbit procedure (110). However, shortening of only 1-1.5 cm has been reported for about 85% of patients, which is rarely the cause for post-operative sexual dysfunction (108,111). Patients often perceive the loss of length as greater than it actually is (109,110). It is therefore advisable to measure and document the penile length peri-operatively, both before and after the straightening procedure, whatever the technique used. Only one modification of the Nesbit procedure has been described (partial thickness shaving instead of conventional excision of a wedge of tunica albuginea) (112).

Plication procedures actually share the same principle as the Nesbit operation but are simpler to perform. Many of them have been described as Nesbit modifications in the older literature. They are based on single or multiple longitudinal incisions on the convex side of the penis closed in a horizontal way, applying the Heineke-Miculicz principle, or plication is performed without making an incision ((113-118). Another modification has been described as the '16 dot' technique with minimal tension under local anaesthesia (119). The use of non-absorbable sutures reduced recurrence of the curvature. Results and satisfaction rates are similar to the Nesbit procedure (104). However, a lot of different modifications have been described and the level of evidence is not sufficient to recommend one method over the other.

*4.4.2 **Penile lengthening procedures***

Tunical lengthening procedures entail an incision in the short (concave) side of the tunica to increase the length of this side, creating a tunical defect, which is covered by a graft. However, plaque removal may be associated with high rates of post-operative erectile dysfunction due to venous leak (120).

Devine and Horton introduced dermal grafting in 1974 (121). Since then, a variety of grafting materials and

techniques have been reported (Table 2) (122-136). Unfortunately, the ideal material for grafting has yet to be identified. In addition, grafting procedures are associated with erectile dysfunction rates as high as 25%. Despite excellent initial surgical results, graft contracture and long-term failures resulted in a 17% re-operation rate (137). Vein grafts have the theoretical advantage of endothelial-to-endothelial contact when grafted to underlying cavernosal tissue. Saphenous vein is the most common vein draft used, followed by dorsal penile vein (104). In the latter case, a secondary incision for graft harvesting is avoided. Post-operative curvature (20%), penile shortening (17%) and graft herniation (5%) have been reported after vein graft surgery (122-124). Tunica vaginalis is relatively avascular, easy to harvest and has little tendency to contract due to its low metabolic requirements (126). Dermal grafts are commonly associated with contracture resulting in recurrent penile curvature (35%), progressive shortening (40%), and a 17% re-operation rate at 10 years (138). Cadaveric pericardium (Tutoplast®) offers good results by coupling excellent tensile strength and multi-directional elasticity/expansion by 30% (129). In a retrospective telephone interview, 44% of patients with pericardium grafting reported recurrent curvature, although most of them continued to have successful intercourse and were pleased with their outcomes ((129,138). Small intestinal submucosa (SIS, a collagen-based xenogenic graft derived from the submucosal layer of the porcine small intestine) has been shown to promote tissue-specific regeneration, and supports the growth of endothelial cells. Small intestinal submucosa acts as a scaffold to promote angiogenesis, host cell migration and differentiation, resulting in tissue structurally and functionally similar to the original. It has been used successfully to repair severe chordee and Peyronie's disease, without significant contraction or histological alterations, but data are limited (133).

Tunical preferably incision with grafting offers an excellent surgical option for men with curvatures over 60º as well as patients with an hourglass deformity and good erectile function that are willing to risk a higher rate of post-operative erectile dysfunction (139). The presence of pre-operative erectile dysfunction, the use of larger grafts, age more than 60 years, and ventral curvature are considered poor prognostic factors for functional outcome after grafting surgery (106). Although the risk for penile shortening is significantly less compared to the Nesbit or plication procedures, it is still an issue and patients must be informed accordingly (104). The use of a penile extender device on an 8- to 12-hour daily regimen has been advocated as an effective and safe way to the loss of penile length in patients operated on for Peyronie's disease (140).

Table 2: Types of grafts used in Peyronie's disease surgery

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

*4.4.3 **Penile prosthesis***

Penile prosthesis implantation is typically reserved for the treatment of Peyronie's disease in patients with erectile dysfunction, especially when they are not responders to phosphodiesterase type 5 inhibitor (PDE5i)

(104). Although all types of penile prosthesis can be used, the implantation of inflatable penile prosthesis seems to be most effective in these patients (141).

Most patients with mild-to-moderate curvature can expect an excellent outcome simply by cylinder insertion. In cases of severe deformity, intra-operative 'modelling' of the penis over the inflated cylinders (manually bent on the opposite side of the curvature for 90 seconds, often accompanied by an audible crack) has been introduced as an effective treatment (142,143). If there is a residual curvature of less than 30°, no further treatment is recommended, as the prosthesis will act as a tissue expander and will result in complete correction of curvature in a few months (142). While this technique is effective in most patients, a Nesbit/plication procedure or plaque excision/incision and grafting may be required in order to achieve adequate straightening (144-146).

The risk of complications (infection, malformation, etc.) is not increased compared to the general population. However, a small risk of urethral perforation (3%) has been reported in patients with 'modelling' over the inflated prosthesis (143).

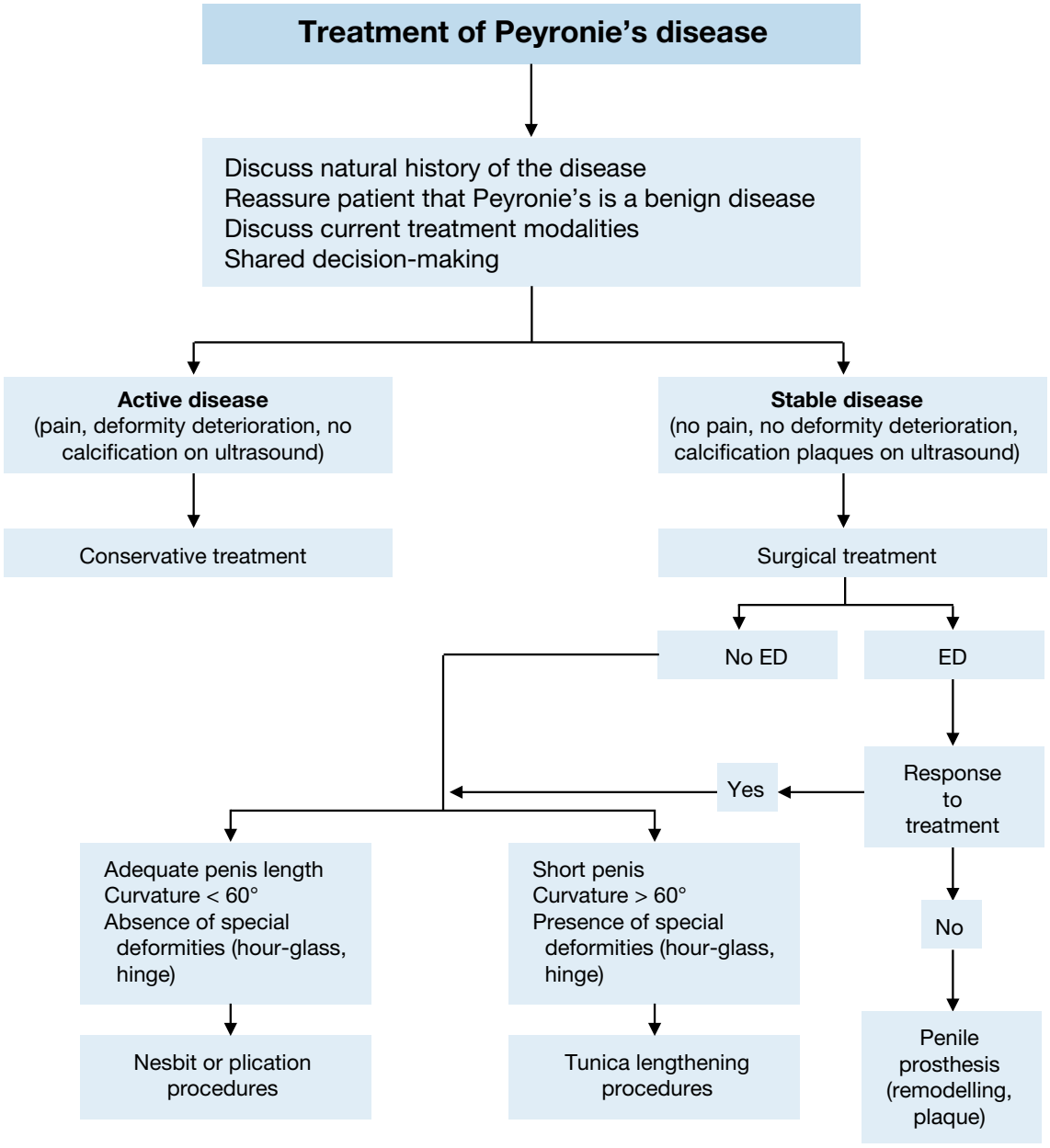
Table 3: Results of surgical treatments for Peyronie's disease (data from different, non-comparable studies) (108,110-136,138,139)

	Tunical shortening procedures		**Tunical lengthening procedures**
	Nesbit	**Plication**	**Grafts**
Penile shortening	4.7-30.8%	41-90%	0-40%
Penile straightening	79-100%	58-100%	74-100%
Persistent or recurrent curvature	4-26.9%	7.7-10.6%	0-16.7%
Post-operative erectile dysfunction	0-13%	0-22.9%	0-15%
Penile hypoesthesia	2-21%	0-21.4%	0-16.7%
Technical modifications	1	At least 3	Many types of grafts and techniques used

*4.4.4 **Treatment algorithm***

The decision on the most appropriate surgical procedure to correct penile curvature is based on pre-operative assessment of penile length, the degree of the curvature and erectile function status. If the degree of curvature is less than 60°, penile shortening is acceptable and the Nesbit or plication procedures are usually the method of choice. This is typically the case for congenital penile curvature. If the degree of curvature is over 60° or is a complex curvature, or if the penis is significantly shortened in patients with a good erectile function (with or without pharmacological treatment), then a grafting procedure is feasible. If there is erectile dysfunction, which is not responding to pharmacological treatment, the best option is the implantation of an inflatable penile prosthesis, with or without an associated procedure over the penis (modelling, plication or even grafting plus the prosthesis). The treatment algorithm is presented in Figure 1.

Figure 1: Treatment algorithm for Peyronie's disease



ED = erectile dysfunction.

The results of the different surgical approaches are presented in Table 3. It must be emphasised that there are no randomised controlled trials available addressing surgery in Peyronie's disease. The risk of erectile dysfunction seems to be greater for penile lengthening procedures (32,104). Recurrent curvature implies either failure to wait until the disease has stabilised, a reactivation of the condition following the development of stable disease, or the use of re-absorbable sutures that lose their strength before fibrosis has resulted in acceptable strength of the repair (104). Accordingly, it is recommended that only non-absorbable sutures or slowly reabsorbed absorbable sutures be used. Although with non-absorbable sutures, the knot should be buried to avoid troublesome irritation of the penile skin, this issue seems to be alleviated by the use of slowly re-absorbed absorbable sutures (110). Penile numbness is a potential risk of any surgical procedure involving mobilisation of the dorsal neurovascular bundle. This will usually be a neuropraxia, due to bruising of the dorsal sensory nerves. Given that the usual deformity is a dorsal deformity, the procedure most likely to induce this complication is a lengthening (grafting) procedure for a dorsal deformity (104).

Guidelines recommendations on surgical treatment for penile curvature	LE	GR
Surgery is indicated when Peyronie's disease is stable for at least 3 months (without pain or deformity deterioration), which is usually the case after 12 months from the onset of symptoms and intercourse is compromised due to deformity.	3	C
Penile length, curvature severity, erectile function (including response to pharmacotherapy in case of erectile dysfunction) and patient expectations must be assessed prior to surgery.	3	C
Tunical shortening procedures, especially plication techniques are the first treatment options for congenital penile curvature and for Peyronie's disease with adequate penile length, curvature < 60º and absence of special deformities (hour-glass, hinge).	2b	B
Grafting techniques are the preferred treatment option for patients with Peyronie's disease with no adequate penile length, curvature > 60º and presence of special deformities (hour-glass, hinge).	2b	B
Penile prosthesis implantation, with or without any additional procedure (modelling, plication or grafting), is recommended in Peyronie's disease patients with erectile dysfunction not responding to pharmacotherapy.	2b	B

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6. ABBREVIATIONS USED IN THE TEXT

This list is not comprehensive for the most common abbreviations.

EAU	European Association of Urology
EMDA	transdermal electromotive drug administration or electromotive drug administration
SWL	shock wave lithotripsy
GR	grade of recommendation
IIEF	international index of erectile function
LE	level of evidence
MeSH	Medical Subject Headings
PDE5i	Phosphodiesterase type 5 inhibitors

Conflict of interest

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