

# Research Review

## EDUCATIONAL SERIES

### Dupuytren's contracture and Peyronie's disease

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**Independent commentary**  
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Mr Darren Katz is the Medical Director at Men's Health Melbourne and a Urological Surgeon, prosthetic surgeon and male fertility microsurgeon. He has several clinical affiliations including Westen Health, Epworth Health Care, Cabrini Hospital and Holmesglen Private Hospital.

As well as completing training as a general urologist, he has spent 2 years at world-leading hospitals in New York, Memorial Sloan-Kettering Cancer Center and Weill-Cornell Medical Centre, completing sub-speciality urological fellowships in andrology, urological prosthetics, male voiding dysfunction, incontinence and male infertility.

Mr Katz is heavily involved with research and academics and has been awarded both national and international grants and scholarships. He has extensively published on a wide range of urological topics and is a reviewer for many of the leading urological journals. Mr Katz has been an invited faculty member for numerous urological workshops to teach other urologists and trainee urologists about some of the latest surgical techniques and advancements in urology.



**Independent commentary**  
by Associate Professor  
David Hunter-Smith

David Hunter-Smith is a Plastic, Reconstructive and Hand surgeon from Melbourne.

He has a special interest in Dupuytren's disease and introduced needle fasciotomy into his practice in 2005. He was a principal site investigator in the Xiaflex multi-cord study and has been using collagenase since its release in the Australian market.

He is a Clinical Associate Professor at Monash University and heads the Peninsula health care networks Dupuytren's clinic.

He has injected over 400 patients with Xiaflex®, has established a comprehensive data collection tool, and is researching the safety and efficacy of the use of Xiaflex® in clinical practice.

#### Abbreviations used in this issue:

**ANOVA** = analysis of variance; **AUA** = American Urology Association;  
**DC** = Dupuytren's contracture; **LOCF** = last observation carried forward;  
**HRQoL** = health-related quality of life; **MITT** = modified intent-to-treat;  
**MP** = metacarpophalangeal; **PD** = Peyronie's disease;  
**PIP** = proximal interphalangeal; **TGA** = Therapeutic Goods Association.

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## Introduction

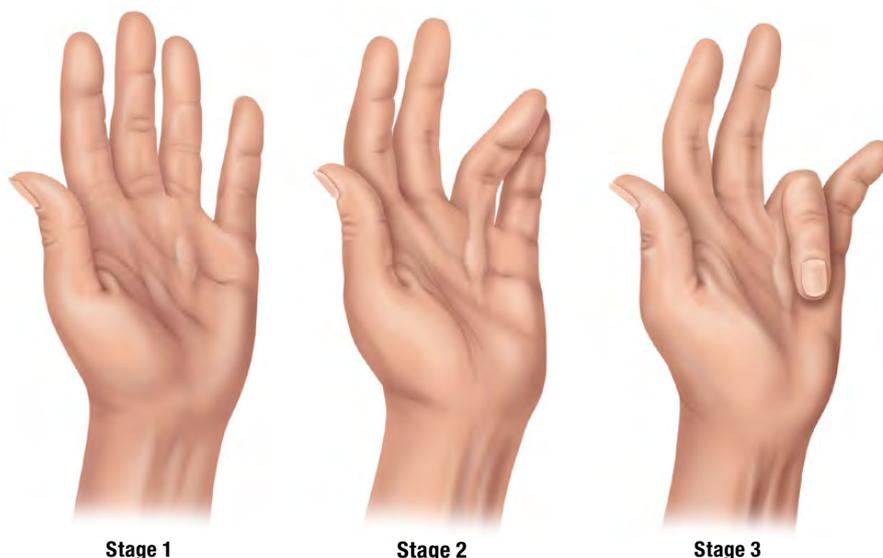
Fibroproliferative diseases are characterised by excessive connective tissue accumulation and slow, but continuous, tissue contraction that lead to progressive deterioration in the normal structure and function of the affected organ(s).<sup>1</sup> Idiopathic pulmonary fibrosis, hepatic cirrhosis, myelofibrosis, systemic sclerosis, hypertrophic scars, keloids, Ledderhose disease, frozen shoulder syndrome, Dupuytren's contracture (DC), and Peyronie's disease (PD) are examples of fibroproliferative disorders. This review will focus on the pathophysiology and treatment of DC and PD.

Tissues from patients with either disease demonstrate a similar pattern of alterations in the expression of certain gene families, suggesting that the two diseases share a common pathophysiology.<sup>2</sup> Although the exact pathophysiology of DC and PD is unclear, an abnormal or exaggerated wound-healing response may be involved, with fibroblast proliferation, cytokine and growth factor expression, and collagen deposition in connective tissue occurring.<sup>3-6</sup> A fuller explanation of the pathogenesis of each disease is given below.

Given the similarities in pathology and genetic drivers of these two conditions,<sup>2,7</sup> it is not surprising that these conditions are commonly comorbid.<sup>5,8,9</sup> In one study of 415 male subjects with PD, 22.1% also had DC.<sup>9</sup> In another study in 140 men with DC, 26% reported PD-like symptoms.<sup>8</sup>

## Dupuytren's contracture

DC involves pathologic collagen production and deposition affecting the palmar fascia.<sup>10-13</sup> It begins with palpable nodules in the palm which develop into a collagen cord. The cord thickens and shortens over time leading to debilitating digital contractures, particularly of the metacarpophalangeal (MP) joints or the proximal interphalangeal (PIP) joints. The ring and little fingers are most commonly affected.



**Figure 1.** Stages of Dupuytren's contracture.

Stage 1. The condition generally starts as a small lump in the palm of the hand, often just under the digit on the palmar crease.

Stage 2. The disease spreads up the fascia and into the fingers, leading to the development of a fibrous cord.

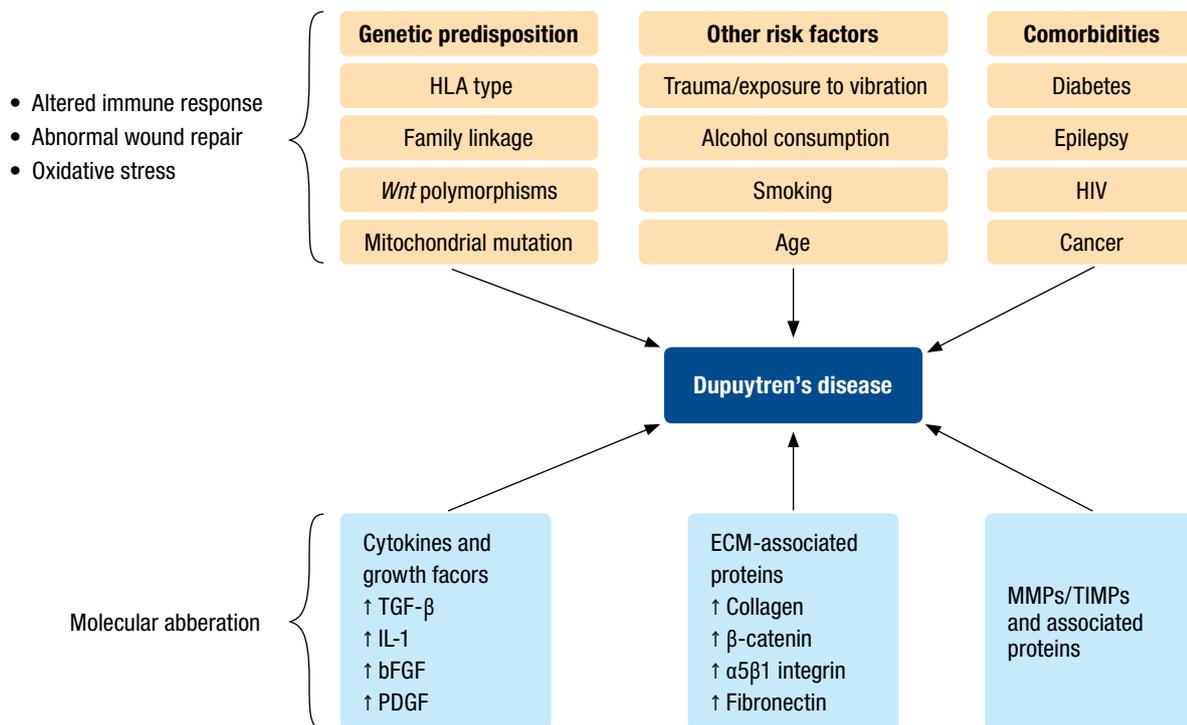
Stage 3. The disease spreads up the fingers, eventually creating a tight cord. Consequently, the fingers are forced to progressively bend, effecting an irreversible contracture.

Source & copyright: Renee Cannon MA

The prevalence of DC varies across different geographical regions (ranging from 0.2% to 56%).<sup>14,15</sup> However, DC disease is most often found in Caucasians of Northern European descent, is more common in males than females, and its prevalence increases with age.<sup>16,17</sup>

The aetiology of DC is not clear, but it appears that genetic and environmental factors are involved.<sup>14,18-20</sup> A genetic predisposition appears to be the reason for its increased prevalence in men of Northern European ancestry.<sup>21</sup> DC has been associated with smoking,<sup>16,22</sup> diabetes,<sup>23,24</sup> human immunodeficiency virus infection,<sup>25</sup> epilepsy,<sup>24</sup> liver disease,<sup>24</sup> and a history of hand trauma and vibratory work.<sup>26,27</sup>

The complex aetiology is reflected in a multi-factorial pathophysiological model (**Figure 2**, page 2).<sup>19,20</sup>



**Figure 2.** Pathogenesis of Dupuytren's contracture.

bFGF=basic fibroblast growth factor; ECM=extracellular matrix; IL=interleukin; MMP=matrix metalloproteinase; PDGF=platelet-derived growth factor; TGF = transforming growth factor; TIMP=tissue inhibitors of metalloproteinase.  
Source: Mandel DR, et al. Int J Clin Rheumatol. 2014;9(2):217-225.

The pathophysiology of DC involves fibroblast proliferation, collagen deposition and myofibroblast contraction driven by various growth factors (**Figure 2**).<sup>4, 13, 19</sup> The potential involvement of an immune response and oxidative stress in the development of DC is supported by reported alterations in levels of immune cells, growth factors and cytokines.<sup>12, 20</sup> Smoking, diabetes, alcohol consumption and aging may lead to oxidative stress and ischemia of the palmar fascia.<sup>20</sup>

The early stage of the disease is characterised by myofibroblast proliferation (resulting in nodule formation).<sup>4, 19</sup> In the contractile stage, nodules tend to regress spontaneously and myofibroblasts become arranged around the major areas of stress within the nodule, forming a cord. The cord is thought to be the result of increased synthesis of types I and III collagen and/or inhibition of endogenous human collagenase activity resulting in increased collagen deposits.<sup>19</sup> The cord is relatively avascular, acellular, and collagen-rich with few myofibroblasts.<sup>4</sup> In normal palmar fascia, type I collagen predominate, but in tissue affected by DC the predominant form is type III collagen.<sup>28, 29</sup>

DC impacts patients' health-related quality of life (HRQoL) and results in both psychosocial and physical consequences.<sup>30, 31</sup> The impaired hand function in patients with DC can limit normal activities at home (e.g. washing and dressing), in the workplace (e.g. manual labour) and in recreational and social interactions (e.g. sports, shaking hands).<sup>32, 33</sup>

### Comment from DC expert

DC can lead to significant functional hand impairment through loss of range of movement. The functional impairment affects activities of daily living that are commonly measured by the use of Dupuytren specific patient reported outcomes measures (PROMS). Examples include the Unite Rheumatologique des Affections de la Main Scale (URAMS, Beaudreuil et al., 2011), a patient-reported functional measure for Dupuytren's disease which contains 9-items and scored between 0 to 45; and the Southampton Dupuytren Scoring Scheme (SDSS, Mohan et al., 2014), a disease specific scoring system for DC with 5 categories of questions and scored between 0 and 20.

DC commonly affects individuals of increasing age. Males are more commonly affected than females. Males typically present at a mean age of 55 compared to 65 for females. The inheritance of DC is thought to be of an autosomal dominant pattern. Patients with a strong family history have a strong diathesis

and present earlier in life with more aggressive disease. Despite ongoing research, the exact aetiology of DC still remains unknown. With the unravelling of the genome, the genome-wide association study (GWAS) has identified at least 20 genes associated with DC and there is emerging evidence to suggest that DC is a predictor of poor health in general. A positive family history is usually identified in over 80% of patients, particularly individuals of Northern European descent. The concept of the disease being a disease of Vikings, stems from the theory that a genetic mutation occurred in middle Europe, sometime between 1200 and 200 BC, and then by observing patterns of Viking movement it was incorrectly attributed to them. Although there is no basis to the disease being truly the "Vikings disease" it is a notion that often resonates with people who suffer from the condition.

The incidence of DC varies between 4 and 20%, depending on the population demographics studied. Surgeons who treat people with DC always try to assess the person's diathesis (or tendency to suffer from the condition). Patients with a strong family history, bilateral disease patterns, rapid growth, radial sided disease, foot involvement etc. have more aggressive disease and a "stronger diathesis". The strength of the diathesis influences decision making, with stronger diatheses often requiring more aggressive treatments at an earlier stage than those with a weak diathesis.

People with DC typically present in a classical way that is easy to diagnose clinically without the need for special tests.

The disease affects the palmar and digital fascial structures of the hand, with the ring and little finger being the most commonly affected digits. Clinically, we examine hands affected by the disease and assess not only the degree of contracture, but also the "bulkiness" of disease (logs vs. twigs – a term coined by Dr David Warwick). Small "twigs" of disease are much easier to treat than large, bulky "logs" of disease.

There is much heterogeneity in the presentation and pattern of disease between people who suffer from the condition which makes treatment difficult to prescribe, particularly as one solution rarely fits all. The treatment paradigm has not changed over decades, since Tubiana described 4 principles in the 1970's: correct the deformity, avoid complications, shorten the postoperative recovery and prophylactically prevent recurrences. However, the available treatment

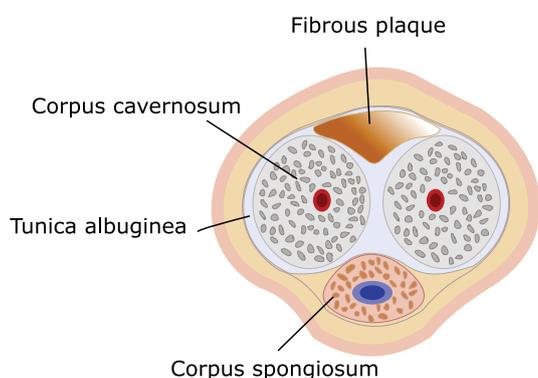
choices have expanded considerably over time. It is now the job of all hand surgeons to match the correct treatment choice with the pattern and diathesis of disease. As hand surgeons, it is incumbent upon us to "maintain hand function and do no harm". In view of this, the analysis and study of patient reported outcome measures (PROMS) is vital to establish the best ongoing treatments for this disease.

From a clinical perspective, the burden of disease from DC is high. DC is not a cancer and, as such, receives limited research funding as opposed to other conditions. However, it still remains the most common fibroproliferative disorder that affects the human.

The epigenetics of DC is being studied at a number of clinical laboratories around the globe. Novel therapies are being investigated and it is likely that there will be an emergence of new and exciting therapies within the next decade to enhance the non-surgical treatment of this condition.

## Peyronie's disease

PD is a localized connective tissue disorder characterised by changes in collagen composition in the tunica albuginea.<sup>6</sup> These changes may result in an abnormal scar formation known as Peyronie's plaque, which is typically a palpable lump under the skin (**Figure 3**).<sup>34</sup>



**Figure 3.** Cross-sectional view of a penis with a dorsally located plaque.

The active phase of the disease is associated with penile pain or discomfort with or without an erection.<sup>5</sup> Penile induration may or may not be manifest. The plaque(s) and penile deformities may not be fully developed at this stage. The pain and progressive deformity may cause distress and may compromise erectile function.<sup>3,6</sup> During the stable phase of the disease, symptoms will have been clinically unchanged for at least three months. Pain with or without erection is rare, and it is typically mild. Curvature of the penis may be uniplanar or biplanar. Plaque(s) may be palpable or apparent on ultrasound. The patients typically present with a dorsal, dorso-lateral, or ventral penile deformity.<sup>6</sup>

Estimates of the prevalence of PD in the general population are varied, because studies have been carried out in different age groups and in different subpopulations of men such as older men undergoing prostate cancer screening, men with diabetes mellitus, or men with erectile dysfunction, rather than in men in the general population.<sup>35-41</sup> The prevalence of penile plaque in populations screened by trained examiners has been reported as being as high as 7% to 9%,<sup>37,38</sup> although the percentage of these patients who present for treatment is much smaller.<sup>42</sup> PD is more common in older men, but it has also been reported in young men.<sup>43</sup> It is estimated that 448,000 males aged  $\geq 18$  years may be affected by PD in Australia.<sup>44</sup> It has been hypothesized that the pathophysiology of PD involves an interplay of microtrauma and wound-healing disruptions.<sup>6,45-47</sup> Trauma causes the release of fibrin deposition, which initiates a local wound healing response. Following the infiltration of neutrophils and macrophages, the synthesis of transforming growth factor  $\beta$  (TGF- $\beta$ 1) is upregulated and the production and deposition of collagen by fibroblasts and myofibroblasts is increased.<sup>45,46,48</sup> TGF- $\beta$ 1 also promotes plaque formation by inhibiting collagenase and stimulating the production of reactive oxygen species.<sup>47</sup> Reactive oxygen species further drive type III collagen deposition and possible calcification.<sup>6,47,49,50</sup>

PD can result in significant physical and psychological morbidity.<sup>51-54</sup> As well as encountering pain and physical deformity, men may experience emotional distress, depressive symptoms, and relationship difficulties.<sup>51,52</sup> Men may have a lowered body image, self-esteem, and may lack sexual confidence, or the ability to initiate sex.<sup>53</sup> Relationships are often impacted negatively.<sup>53</sup> Men with PD have reported feeling isolated, especially if they find it difficult to communicate with their healthcare professionals or partners about PD.<sup>54</sup>

## Comment from PD expert

PD is an under-diagnosed disease. This can be attributed to the nature of the condition and the hesitancy for patients with sexual concerns to seek treatment.

Despite the high prevalence (about 5-10% of the adult male population), the underlying aetiologies and precise pathogenesis are still under investigation. The current view is that it is an interplay of genetically susceptible patients, who undergo micro-/macro-trauma to the penis which results in abnormal wound healing. Certain groups of patients are also at higher risk including diabetics and patients who have had major pelvic surgery.

The diagnosis of PD is a clinical one. Essentially almost every patient with new onset penile curvature in the erect penis and a "lump" in the penis palpated in the flaccid state has PD. Other differential diagnoses are rare.

For patients that have had penile curvature "for as long as they recall" probably have congenital penile deviation for which the treatment algorithm is different. These patients are usually younger and have a higher prevalence of ventral curvature.

Whilst imaging can help support the diagnosis, this really should only be ordered by a urologist. In my clinic, for certain patients, I perform a penile duplex ultrasound and curvature assessment in my rooms. I inject a vaso-active agent into the penis to allow the patient to get an erection so I can assess objectively the curvature and associated deformities. I then undertake a penile duplex ultrasound to assess plaque characteristics and measure the patient's haemodynamic erectile function. Using all of these parameters, I can then make an informed recommendation as to whether treatment is needed, and if so, which type.

PD is an important diagnosis to make as, in a significant proportion of men, it can take a large psychosocial toll on the patient. I have certainly seen patients who avoid sexual intimacy or even some in whom their relationship has broken down, which can be attributed, at least in part, to PD.

## Treatment

There is no definitive cure for the pathological process present in either DC or PD. Management of these diseases is dependent on disease progression and degree of deformity, and not all people with DC or PD seek or require treatment.

Observation may be appropriate in patients with painless mild, early stage DC stages with minimal contracture and no functional impairment.<sup>55</sup> Similarly, for a patient with PD, thoughtful counselling regarding the nature of the disease and its typical course may be sufficient to alleviate concerns, and the patient may choose not to pursue further treatment.<sup>6</sup>

The American Urological Association (AUA) recommends oral non-steroidal anti-inflammatory medications for patients with PD in need of pain management.<sup>6</sup> The AUA does not recommend the use of oral treatments such as vitamin E, procabazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine in the treatment of PD. Similarly, electromotive therapy with verapamil is not recommended.

Historically, surgery has been the mainstay of treatment for patients with moderate to severe forms of either disease.<sup>3,6,56-58</sup>

- For patients with moderate-to-severe DC, common surgical procedures include surgical fasciectomy (excision of the Dupuytren's cord), or open or percutaneous needle fasciotomy (division of the cord by fine blade or needle).<sup>56-58</sup>
- For patients with PD, international guidelines recommend surgery be considered in men with stable disease (once the penile deformity has remained stable and painless for at least 3 months).<sup>3,6</sup> Surgical procedures include penile plication (shortening the convex side), graft surgery (lengthening the concave side of the tunica albuginea by incision or partial excision of the plaque with the use of various graft materials for closure of the defect), and penile prosthesis implants with or without adjunctive measures, such as penile remodelling, plication and grafting.<sup>59</sup>

Recurrence of DC or PD can occur after surgery.<sup>60, 61</sup> Moreover, surgical treatments for these diseases have limitations and potential complications.<sup>62</sup> Penile plication can cause perceptible length loss and patients can usually palpate the tunical sutures under the skin. Graft surgery for PD is highly complex and only offered by a limited number of sub-specialist surgeons in Australia. This surgery does carry the risks of erectile dysfunction and graft contracture resulting in curvature recurrence

Recently, collagenase clostridium histolyticum (CCH) has been developed and approved as a less invasive treatment for these disorders.<sup>63, 64</sup>

- In patients with DC, CCH is injected into the affected cord, and the treated joint is then manipulated to attempt cord rupture.<sup>64</sup> Manipulation should happen from 24 to 72 hours after injection into the cord.
- International guidelines recommend intra-lesional CCH in combination with modelling by the clinician and by the patient for the reduction of penile curvature in patients with stable PD, penile curvature >30° and <90°, and intact erectile function (with or without the use of medications).<sup>6</sup>

### Comment from DC expert

The treatment for DC is multifaceted with both surgical and non-surgical alternatives.

Open surgery in the form of fasciectomy (limited or with skin grafting) has been, historically, the mainstay treatment for people suffering from DC.

The most common surgical procedure performed in Australia is limited fasciectomy. This is where the skin is incised, the underlying diseased fascia is removed and the skin is closed and rearranged, usually with the formation of Z-plasty scars.

If the disease is more aggressive then the skin is also removed, along with the underlying fascia, and skin grafts are applied. Historically, an open palm technique was commonly used, which is called the McCash technique. This is where large incisions are made across the palm, the underlying disease removed and the palm is left open to heal by secondary intention.

Although surgery is very successful in correcting the deformity, the complication rates are higher with open surgery and the postoperative recovery can be prolonged. Around 5% of patients who undergo surgery have a very prolonged recovery period, which has made it unattractive to many patients. Surgery, however, does provide the best prophylactic prevention of recurrence.

The less invasive techniques include simple fasciotomy (needle fasciotomy or needle aponeurotomy). This was popularised by the French in the 1970's. The bevelled edge of a hypodermic needle is inserted beneath the skin and the diseased cords are divided, simply releasing the contracture. This can be very successful if used carefully in patients with slowly progressing disease and bands of tissue that are easy to palpate and feel.

The concern with needle fasciotomy is that the technique is more difficult to learn and there is an increased risk of nerve injury. The recovery from needle fasciotomy is fast, however the prophylactic prevention of recurrence is poor and the disease is expected to recur.

Because of the increased complication profile and longer postoperative recovery from the surgical options, the non-invasive techniques have emerged and are particularly appealing to people who suffer from the condition. There have been a number of studies that have looked at the trade-offs that patients will accept when making a decision about the treatment options for DC. Dr Steven Hovius from the Netherlands has studied this extensively, and his research, along with my experience is that patients will accept a high rate of recurrence to avoid complications and prolonged recovery when making their decisions about the best treatment for them.

Collagenase therapy provides a relatively non-invasive option that provides good release of contracture, a low complication profile, a fast recovery and a reasonable prophylactic prevention of recurrence.

Other non-surgical options that have been explored for DC include pharmacological therapies, such as steroid injections, vitamin A and E applications, 5-fluorouracil treatment, physical therapy and radiotherapy. There is little evidence that these treatments aid anything but the very earliest of presentations.

### Comment from PD expert

For many patients with PD, there is a long delay, sometimes years, before they build up the courage to seek specialised treatment. Many of these patients, come into my clinic after having tried various, mostly ineffective, therapies which they either bought online or received from other medical practitioners who may not be up to date with the latest advancements in PD therapy.

Recently there have been two publications, which have summarised the evidence and given the current best-practice management recommendations for PD.<sup>3, 6</sup> These are essential reading for any clinician with an interest in treating PD.

A key take home message is that not every patient with PD needs treatment. Essentially, patients that are bothered by their penile curvature in the erect state, especially if it is interfering with sexual intercourse, are the best candidates for treatment. In the acute phase, which can last from a few weeks to about 2 years, treatments are aimed at arresting further curvature development. While there are some therapies for patients in the acute phase of PD, many of these are not based on a solid clinical evidence base.

In the chronic phase of the condition, the goal of treatment is to improve penile curvature. No intervention can cure PD but certainly there are treatments that greatly improve a patient's quality of life and sexual functioning. Prior to intra-lesional CCH, the best evidence for treating PD in the chronic phase was surgery. Whilst surgery is still an important strategy for some patients, almost every surgical procedure has some limitations and potential complications.

### Collagenase clostridium histolyticum

Collagenase clostridium histolyticum (CCH) consists of two microbial collagenases in an approximate 1:1 mass ratio that have been isolated and purified from the fermentation of *Clostridium histolyticum* bacteria: collagenase AUX I (Clostridial Type I collagenase) and collagenase AUX II (Clostridial Type II collagenase) (Figure 4).<sup>47, 63</sup>

CCH selectively targets type I and III collagen fibres that generate the pathological constriction in DC and curvature in PD.<sup>47</sup> CCH hydrolyses type I and type III collagen into smaller peptides which endogenous human collagenases can further degrade. CCH did not cause structural damage to arteries, nerves or large veins which contain type IV collagen in *in vitro* or *in vivo* studies. The collagenases (AUX I and AUX II) work synergistically to provide hydrolysing activity towards collagen (Figure 4).<sup>47, 63</sup> CCH may also suppress fibroblast adhesion and proliferation, and decrease expression of TGF-β1, smooth muscle actin, and fibronectin.<sup>47</sup>

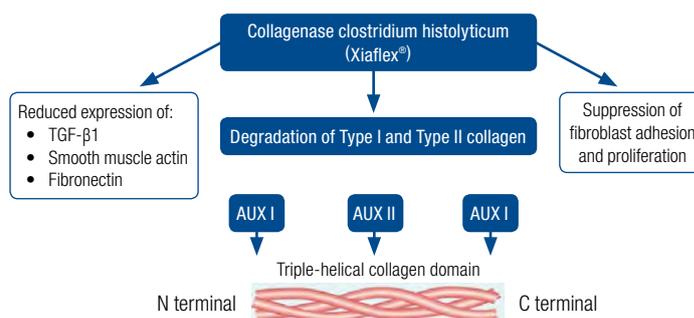


Figure 4. Mechanism of action of CCH.

AUX = collagenase Clostridium histolyticum class; TGF-β1 = transforming growth factor-β1.

CCH has received Therapeutic Goods Association (TGA) approval for:

- The treatment of DC in adult patients with a palpable cord (approved November 2013),<sup>63</sup>
- The treatment of adult men with PD with a palpable plaque and curvature deformity of at least 30 degrees at the start of therapy (approved March 2016).<sup>63</sup>

No other pharmaceutical therapy has TGA approval for DC or PD. CCH is not listed on the Pharmaceutical Benefits Scheme.

CCH is only to be administered by qualified doctors who are<sup>63</sup>:

- experienced in the diagnosis of DC, experienced in surgical management and in injection procedures of the hand; or;
- experienced in the diagnosis and treatment of male urological diseases (e.g., urologists and sexual health physicians), and;
- have been appropriately trained in the correct administration of the product.

## Clinical studies involving collagenase clostridium histolyticum

### Dupuytren's contracture

CCH was effective and well tolerated in phase III clinical trials (CORD I<sup>65</sup> and II<sup>66</sup>) and in open-label studies (JOINT I and II<sup>67</sup>) and post-marketing studies.<sup>68,69</sup> Moreover, the 5-year CORDLESS trial demonstrated that the response was maintained for approximately half of the joints successfully treated (to  $\leq 5^\circ$  residual contracture) with CCH.<sup>70</sup> The adverse events reported during the clinical studies were mild to moderate. Local injection-site reactions were most commonly reported and were mostly mild to moderate in severity and generally subsided within 1-2 weeks post-injection.<sup>63</sup> Flexor tendon ruptures have occurred after CCH injection. CCH should be injected only into the collagen cord with a metacarpophalangeal or proximal interphalangeal joint contracture.<sup>63</sup>

In the CORD trials, the cord affecting the selected primary joint received up to three injections of CCH or placebo, with each injection up to 4 weeks apart. The mean number of injections required was 1.5.<sup>63</sup>

### Comments from DC expert

Collagenase therapy was introduced in Australia in late 2013 and licenced by the Therapeutic Goods Administration (TGA) for the treatment of DC.

In Australia, suitably qualified hand surgeons and rheumatologists (who have participated in previous trials), have access to the drug for the treatment of DC. The benefits of the injection are that it usually provides an excellent correction of deformity, particularly if the disease is treated early. It has a favourable complication profile, a shorter postoperative recovery and a reasonable prophylactic prevention of recurrence. Unfortunately, the drug is not currently listed on the PBS and, thus, people with DC who want to receive collagenase injections for their disease either fund it privately or attend one of the emerging public hospital collagenase clinics (currently 24 public clinics in Australia).

In the past, surgeons were reluctant to offer open surgical fasciectomy until the disease was well established and there was a major effect on activities of daily living.

In view of the availability of collagenase therapies and needle fasciotomy techniques, we very much prefer to see patients in the early stages of their disease so that we can correct deformity, limit morbidity and maintain hand function.

The contemporary treatment of the condition should be to, treat patients early, maintain hand function and repeat treatments in the future, if required, to prevent the necessity for more aggressive therapies.

There is now ample evidence to support the use of collagenase for the treatment of DC from a safety and efficacy position.

Common side effects of collagenase include bruising, swelling, minor skin splits and discomfort. The serious but rare adverse events include anaphylaxis and tendon rupture, which have serious consequences to the patient and underpin the decision of the TGA to restrict the use of collagenase to hand surgeons.

### Peyronie's disease

The efficacy of CCH was evaluated in two pivotal trials (IMPRESS I and IMPRESS II) in adult patients with PD.<sup>63,71</sup> Men were given up to four treatment cycles of CCH or placebo, with two injections per cycle and with 6 weeks between each cycle. A penile modelling procedure was performed on patients at the study site 1 to 3 days after the second injection of the cycle. Patients were instructed to perform penile modelling at home for six weeks after each treatment cycle to help disrupt the plaque.

CCH treatment, compared with placebo, significantly improved penile curvature deformity and reduced patient-reported bother associated with Peyronie's disease in these two 52-week, phase III trials. Most adverse reactions were local events of the penis and groin, and the majority of these events were of mild or moderate severity. Most adverse events (79%) resolved within 14 days of the injection. Corporal rupture has been reported in 0.5% of men involved in controlled and uncontrolled PD clinical trials.<sup>63</sup> Patients should be advised to wait two weeks after the second injection of a treatment cycle before resuming sexual activity, provided pain and swelling have subsided.<sup>63</sup>

### Comments from PD expert

With the introduction of intra-lesional CCH, the treatment paradigm has dramatically changed for patients with PD. Intra-lesional CCH, which is essentially a "chemical knife" is the first non-surgical intervention in PD to come to market based on high level of clinical evidence. This gives those of us treating this condition, more confidence in recommending intra-lesional CCH. The randomised, placebo controlled studies, suggest an overall improvement in penile curvature of 34%. It is important to explain to patients that this is the relative percent improvement, not the absolute degree improvement from baseline penile curvature. In addition, 34% is the average – some patients improved more, some less.

In reality, most patients with bothersome PD are potential candidates for intra-lesional CCH. Those patients with plaques that are either heavily calcified, ventrally located or impalpable are not suitable.

When intra-lesional CCH was first introduced, it was seen as a potential alternative to surgery. While this is true for mild-moderate curvature, more recently intra-lesional CCH has been used to "downstage" the severe cases of PD. In general, the more severe the penile curvature, especially if associated with erectile dysfunction, the more complex the surgery needs to be with the attendant increased risks. For such patients, intra-lesional CCH can improve curvature to the point that less aggressive and complex surgery is needed.

However, there are some important downsides to the treatment. The reason why most patients do not choose intra-lesional CCH is because of the cost of the drug. Currently, it is not on the PBS. Also, the treatment course involves multiple injections over several months. Therefore, for patients who are looking for a "quick fix", surgery is recommended. The side effects of the drug are generally minimal and it is a well-tolerated therapy. Most patients do get some bruising but this settles. There are significant complications such as corporal rupture but these are very rare, especially if the patient adheres to the post-injection advice.

The protocol for injections and techniques are beyond the scope of this article, but in short, the sentinel trials involved four cycles of treatment. Each cycle involves two injections and 6 weeks of structured penile modelling exercises. Even amongst my colleague urologists, very few have a sub-speciality interest in PD and regularly administer intra-lesional CCH. In order to know which urologists in your area are happy to treat the condition with CCH you can go to [xiaflex.com.au](http://xiaflex.com.au).

## Conclusions

While neither collagenase injection nor surgery provides a cure for these diseases, CCH represents a clinically efficacious and tolerable option for the non-operative treatment of DC and PD.

### Concluding comments from DC expert

The changing paradigm in the treatment of DC has made it important for people with this condition be assessed by hand surgeons with experience in the use of all modalities to manage DC. This ensures that all treatment options, and better outcomes are made available for people with the condition at all times. We expect that novel therapies will become available with time that will aim treatment at the myofibroblast and extracellular matrix.

### Concluding comments from PD expert

CCH has been a major advancement for patients with PD. Prior to its introduction, surgery was the only reliable treatment available for patients in the chronic phase of the condition. CCH allows patients to choose a non-surgical therapy, which has been demonstrated in large good quality studies to improve penile curvature and bother from the condition. More recently, it has also been observed as an adjunct to surgery to downstage severe cases. In the future, I predict that the indications will expand to include patients in the acute phase of the condition. Currently, there are limited treatment options for patients in this early phase of the condition.

The Clinic Finder provides a list of healthcare professionals who have completed certification training for administering XIAFLEX®, and who have provided consent for their details to be shared. The training site and more information on CCH can be found at [xiaflex.com.au](http://xiaflex.com.au) or at [xiaflexactelion.com.au](http://xiaflexactelion.com.au) (Password: XCF2017). The Clinic Finder may not contain an exhaustive list. Certified healthcare professionals may have their details added on request [act-xiaflex-access-au@its.inj.com](mailto:act-xiaflex-access-au@its.inj.com).

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