

# Update on the management of Dupuytren's contracture.

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### **Abstract**

A degenerative condition of the palmar fascia, Dupuytren's disease (DD) is typified by the production of taut collagenous disease cords that result in chronic contractures of the fingers. The disease is more common in older males who are Caucasian, and its incidence rises with age. Impaired ability to perform daily tasks with the hands is the most frequent complaint from DD sufferers. The aetiology of DD is unknown, and the disease is currently incurable. Surgery is the most popular treatment for developmental disabilities, however it has a high recurrence rate. In an effort to create a new, more potent DD medication, scientists have more recently started looking into the molecular causes of DD. The history and clinical manifestation of the illness will be outlined in this study, with special attention to work.

**Keywords :** *Dupuytren's disease, etiology, clinical presentation, treatment*

### **INTRODUCTION**

Dupuytren's contracture, also known as Dupuytren's disease [DD], is a medical disorder that affects the hand's palmar fascia, causing the affected fingers to flex abnormally.<sup>1</sup> Ledderhose disease, also known as plantar fibromatosis, is a condition in which this illness also affects the plantar fascia. Unlike DD of the palmar fascia, patients with plantar fibromatosis usually do not develop contractures of the afflicted plantar structure. Instead, the disease presents immunohistologically similarly.<sup>2</sup> A person's capacity to participate in both work and leisure

activities may be significantly impacted by DD that affects the hands, which frequently results in dexterity limits. Additionally, patients express concerns about safety, particularly the notion that their finger's permanent flexion will leave it more vulnerable to harm. Last but not least, individuals with DD also voice worries about how their contracture may impact their social interactions, particularly their capacity to shake hands appropriately.<sup>3</sup> It is preferable to repair flexion abnormalities for these reasons. Unfortunately, treatment now focuses only on removing the developed pathologic disease tissue without addressing the underlying pathophysiology due to a lack of a complete understanding of the molecular pathology. When it comes to rehabilitation, the most popular strategy is still surgically excising the diseased chord and then receiving intense postoperative physical therapy.<sup>4,5</sup> Less invasive therapeutic methods, including needle aponeurotomy or enzymatic digestion of the illness cords, have been tried due to the considerable morbidity linked with surgery. But these operations don't work as a cure and come with Having a high recurrence rate.<sup>6</sup> In an effort to create new, more potent therapies for the management of developmental disorders, recent research has started to investigate the genetic underpinnings of illness progression and recurrence. This review aims to: (1) provide an overview of the disease's history and clinical manifestation; (2) highlight recent and emerging advances in conventional and molecular treatments; and (3) investigate the significance of these developments for future research and improved patient care.

### **Prevalence and etiology**

The three factors of age, gender, and ethnicity all affect the occurrence of DD. Males are expected to be affected 7–15 times more frequently than females by this disease, which is thought to be a hereditary dominant condition with varying penetrance.<sup>7</sup> For males, the condition usually manifests after the fourth or fifth decade of life, whereas females typically experience the sickness later in life.<sup>7,8</sup> Despite the fact that primary DD is more common in men, both sexes have roughly the same chance of recurrence following surgery.<sup>7</sup> DD has been documented in newborns and children, despite its rarity.<sup>9–12</sup> There have

only been a few histologically verified examples of DD found in the literature to date, despite the fact that the condition has been documented in infants as young as six months old<sup>11,12</sup>. In this stage of childhood, however, histological confirmation is highly advised to rule out other potential causes of the nodule formation or the digit contractures, or both, such as arthrogryposis, camptodactyly, congenital ulnar drift, and epithelioid sarcoma.<sup>9, 12</sup> Many doctors consider DD in children to be a distinct entity from classical DD due to its relatively low occurrence.

While less common in other areas like Southern Europe, South America, and Asia, DD is common in some Caucasian groups, such as those in Scandinavia, Britain, and Australia.<sup>13, 14</sup> While rare throughout most of Asia, some groups—Japan and Taiwan, in particular—have greater prevalence rates, which are similar to those found in populations in Northern Europe.<sup>15</sup> It has been shown that the prevalence of DD among guys who are over 70 years old and have ancestry from Northern Europe.<sup>16</sup> A DD diathesis is a concept coined by Hueston<sup>13</sup> in 1963 to describe a set of characteristics that would substantially predict the severity of an illness and its recurrence following therapy. Individuals with a positive family history of developmental disorders (DD) and those of Northern European heritage, who often exhibit a younger age of onset, are more likely to acquire DD and experience a more severe disease progression. Hueston<sup>13</sup> further proposed that patients with ectopic lesions (DD outside the palm) and bilateral hand involvement are at higher risk of recurrence and rapid disease development. The management of this condition still heavily depends on how severe a patient's illness presentation is. Numerous comorbidities and socioenvironmental factors have been found to contribute to this illness in addition to hereditary considerations. Research indicates that individuals with specific underlying medical disorders, such as diabetes mellitus<sup>17,18</sup> and epilepsy, may be at a higher risk of developing DD.<sup>19</sup> Alcoholism, or heavy alcohol intake, and smoking are two lifestyle risk factors linked to DD.<sup>20–22</sup> Additional variables that have been linked to the illness include manual labour contributions, hand or wrist damage, history of recurrent hand vibrations, and more. But opinions on these elements' contributions are still divided, and other research hasn't been able to find any connection between, say, trauma and the onset of DD.

### Clinical presentation

Although DD frequently affects both hands, it usually affects

one hand more severely than the other. The thumb and other fingers may also be impacted, but the ring and little fingers are typically the most afflicted.<sup>28</sup> It is thought that the illness begins as a nodule and develops into a cord<sup>29</sup> that, as it ages, contracts and causes the affected digit(s) to permanently flex. The first indications of developmental disorders (DD) are alterations in the skin, like skin pitting.<sup>31</sup> Full-thickness palmar skin retraction into the subcutaneous tissue is the cause of skin pits. The dorsum of the hand may also alter if knuckle pads or Garrod nodes are present.<sup>32</sup> Nonetheless, patients with ectopic illness and bilateral disease are more likely to have these. Such as Peyronie's disease and plantar fibromatosis.<sup>33, 34</sup> Thus, skin pits have been proposed as a more accurate early marker of DD. A palpable soft-tissue lump that is attached to the skin and the underlying palmar fascia is called a nodule, and it is frequently utilised as a characteristic for illness diagnosis.<sup>29</sup> Usually painless, these masses might cause pain when the disease first manifests or if they are linked to tenosynovitis, which is a condition where the flexor tendons become restricted.<sup>35</sup> There are two primary kinds of nodules: digital nodules, which are usually situated at the base of the digits or close to the proximal interphalangeal (PIP) joint, and palmar nodules, which are placed next to the distal palmar crease. As the illness worsens, a chord starts to form as the nodule's protrusion. These cords appear to follow the typical palmar fascial structures, which are known as "bands" when they are in a healthy form. The cord resembles a tendon in appearance and grows more fibrotic as it ages, becoming more noticeable.<sup>36</sup> The unique flexed position of the digits is caused by the mature cord contracting.

The precentral cord, which originates from the palmar fascia's precentral band and is the most often generated cord in the palm, usually causes the metacarpophalangeal (MCP) joint to deform in a flexion manner. The precentral cord rarely moves the neurovascular bundle, while it occasionally bifurcates at the level of the distal palmar crease.<sup>37</sup> Additional cables influencing the palm are the Although they are less common than the precentral cord, the vertical and natatory cords originate from the natatory ligaments and the vertical bands of Legueu and Juvara, respectively.<sup>38</sup> Because the digital and palmar fascias are connected, palmar contractures frequently extend into the digits, where they may cause further flexion abnormalities in the distal interphalangeal (DIP) and PIP joints.

The central, lateral, and spiral cables are the most common types of digital cords.<sup>30</sup> The precentral cord, which originates in the neurovascular bundles' midline and connects to the flexor

tendon sheath, is an extension of the central cord. The MCP and PIP joints may become malformed by this cord, however the neurovascular bundles are rarely moved.

The lateral cord, which is the diseased state of the lateral digital sheath, is a continuation of the bifurcated precentral cord. It affixes to the skin or the tendon sheath close to the Grayson's ligament, in contrast to the central cord. Although it can also affect the DIP joint, this chord typically causes abnormalities in the PIP joint. Sometimes these lateral cords cause the neurovascular bundle to be displaced towards the midline, which makes the surgical technique more difficult. The precentral cord, which originates far from the MCP joint and deep within the neurovascular bundle, is also extended by the spiral cord. The cord in the digit advances superficially to the neurovascular bundle, via Grayson's ligament, and lateral to the neurovascular bundle, involving the lateral digital sheath. When finger contractures are formed, this causes the cord to wrap around the neurovascular bundle and cause the neurovascular bundle to shift superficially, proximally, and centrally. The neurovascular bundle may also become severed during surgery as a result of this displacement.

### Pathophysiology

Even though the exact aetiology of DD is unknown, it is frequently categorised as a fibromatous disorder. Three stages have been identified as part of the pathophysiology of DD: proliferative, involutionary, and residual.<sup>36, 39</sup> Nodule creation, the product of myofibroblast differentiation, fibroblast hyperproliferation, and type I and type III collagen deposition, is what defines the proliferative stage.<sup>36, 39–41</sup> This process ultimately results in the development of the disease cord structure. Myofibroblasts align along the lines of tension in the sick tissue during the involutional stage of the disease progression. It is believed that these cells produce contractile forces that cause the sick tissue to shorten. Later, more collagen deposition is thought to cause the cord to permanently shorten, resulting in joint contractures. Lastly, there is a further rise in type I collagen synthesis during the residual stage.<sup>36, 41</sup> During this stage, the sick cord also gets more acellular due to a rise in myofibroblast apoptosis.<sup>36, 41, 42</sup> The widespread consensus is that the digit contractures associated with developmental disorders are mostly caused by contraction forces generated by myofibroblasts. This notion is supported by a wealth of data that show a temporal relationship between the start of contraction and the formation of myofibroblasts.<sup>43–45</sup> These cells are of fibroblastic lineage,

but they lack other significant smooth muscle markers like myosin. Instead, they express several specific muscle-associated markers, such as calponin and  $\alpha$ -smooth muscle actin, the predominant isoform of actin found in contractile cells called myofibroblasts.

At fibronexus, fibronectin-rich locations, these myofibroblasts establish broad connections with the extracellular matrix (ECM).<sup>47, 48</sup> Strong fibronectin expression is seen in the disease cord tissue, and immunohistological examination indicates that  $\alpha 5$ -1 integrin-fibronectin complexes are interacting with myofibroblasts in the disease cord. From a biological perspective, DD is similar to an over-reaction to wound healing. Early on, the ratio of type III to type I collagen is higher in both wound granulation tissue and DD, and it decreases as the condition progresses.<sup>39</sup> In DD, there is a significant upregulation of transforming growth factor (TGF)- $\alpha$ , a pleiotrophic cytokine released during the inflammatory response of wound healing.<sup>52</sup> It has been demonstrated that the cytokine TGF- $\alpha 1$  stimulates myofibroblast differentiation by inducing  $\alpha$ -smooth muscle and fibroblast proliferation by activating transcription<sup>53</sup> through  $\beta$ -catenin-mediated transactivation. expression of actin.<sup>54</sup> Previous research has demonstrated that whereas  $\alpha$ -catenin is widely distributed throughout the illness cord, patient-matched, phenotypically normal palmar fascia almost completely lacks it.<sup>55</sup> Furthermore, we have shown that TGF- $\alpha 1$  stimulates  $\alpha$ -catenin accumulation while reducing levels of  $\alpha$ -smooth muscle actin in disease cells cultivated on type I collagen to more nearly mimic in vivo settings.<sup>56</sup> TGF- $\alpha 1$  activation of disease cells resulted in increased cell contractility when they were grown in stressed three-dimensional collagen lattices. This was connected with increases in the levels of  $\alpha$ -smooth muscle actin and myofibroblast differentiation.<sup>57</sup> DD is distinguished by the overexpression of TGF-1 as well as platelet-derived growth factor, basic fibroblast growth factor, and epidermal growth factor—that is, physiologically active molecules involved in the different stages of the disease.

### Surgical interventions

The most popular therapy for DD, surgery, is usually taken into consideration when the contracture significantly impairs hand function. Usually, this happens when the PIP flexion contracture or MCP flexion contracture surpasses 30°. There are numerous methods for treating the joint abnormalities and finger contractures linked to this illness. Resection of the afflicted palmar fascia is a standard procedure known as

a palmar fasciectomy. Local, regional, and total fasciectomy are the three primary forms of palmar fasciectomy. The least invasive of the three options is local fasciectomy, which involves cutting off portions of the diseased chord to relieve finger contractures.<sup>61</sup> There is a significant risk of recurrence since the local fasciectomy treatment leaves sick tissue in the hand. Using a regional or partial fasciectomy, which involves removing as much of the damaged fascia as possible, is the more popular method.<sup>62</sup> Comparing this treatment to a local fasciectomy procedure, there is a decreased chance of disease recurrence.<sup>61</sup> A more intrusive surgery called a whole or radical fasciectomy involves removing the palmar and digital fascia.<sup>61</sup> But as compared to partial fasciectomy, this procedure does not have a lower recurrence rate and is frequently linked to higher risks of surgical complications.<sup>61</sup> Fasciotomy has been recommended for less severe diseases that just affect the palmar cords. A fasciotomy is a procedure that divides the damaged chord without removing the affected tissue, thus relieving contractures.

Recurrence of the disease is rather high since the sick tissue is not eliminated.<sup>64</sup> The closed method, also known as a needle fasciotomy or aponeurotomy, is positioning a needle next to the chord and using the needle's sharp, bevelled edge to "slice" the diseased cord in order to remove the contracture.<sup>65,66</sup> Despite being minimally invasive, this operation should be utilised with caution, according to many surgeons, as it puts the flexor tendons and nerves at risk of being severed during the surgical process.<sup>66</sup> As of right now, this method is thought to be useful only for the treatment of mild-to-moderate MCP contractures. The open fasciotomy technique is an alternative to closed fasciotomy. In order to visualise the illness chord, this method entails making an incision in the hand's palm.<sup>67</sup> After then, the contracture can be removed by severing the cord.<sup>67</sup> Although less intrusive than a closed fasciotomy, this treatment offers the advantage of directly visualising the diseased cord, which lowers the chance of injury to the hand's nerves. Dermafasciectomy is advised for the treatment of aggressive or recurring illness. In this lengthy procedure, the damaged fascia is removed together with the skin that covers it, and the skin is then closed using skin grafts.<sup>68,69</sup> The risk of illness recurrence is reduced with dermofasciectomy as opposed to fasci-ectomy alone.

### Physical interventions

Splinting is a common postoperative physical therapy treatment

used to try to enhance long-term extension.<sup>70</sup> Splinting is used to maximise finger extension and function by increasing wound healing and minimising the production of scar tissue, albeit its efficacy is still unknown.<sup>71</sup> Splinting alone, however, is not likely to be a viable treatment option for either reducing finger contractures or slowing the development of the disease. In the early stages of the disease, radiation therapy has also been suggested as a substitute for surgery.<sup>72</sup> Based on certain clinical trials, radiation therapy might be useful in delaying the course of a disease.<sup>72,73</sup> However, the effectiveness of radiation therapy has not been demonstrated with sufficient evidence, and more research is required to determine the possible toxicity and long-term dangers connected to treating a benign illness with localised radiation.

Ultrasound heat therapy is another physical method that has been documented in the literature.<sup>74</sup> The disulfide bonds that hold collagen fibrils together can be broken by routinely using ultrasonography. Ultrasound and physical stretching together have the potential to improve function and decrease the progression of disease.<sup>74</sup> Nevertheless, prospective randomised trials have never been carried out, therefore it is still unknown how beneficial this therapy approach will be in the short- and long-term.

### biological remedies

Finding viable molecular targets for nonsurgical alternative therapy has been the main focus of most DD research due to the high rates of disease recurrence and hazards associated with surgical methods.

Numerous possibilities have been identified with the use of differential gene expression analysis in conjunction with molecular and functional studies of sick tissues and cells. Injecting localised collagenase has become one of the new therapy modalities over the years.<sup>75–77</sup> Type I collagen makes up the majority of the developed disease cords, which leaves them vulnerable to the enzymatic activity of collagenase, which breaks down peptide bonds in collagen fibres. Injection of collagenase into diseased cords has been shown in several studies to reduce finger contracture.<sup>18,75–77</sup> Collagenase injection is an efficient nonoperative treatment to lessen contractures and increase joint mobility in situations of severe illness, according to a recent double-blind, randomised prospective research.<sup>75</sup> While collagenase injection may lessen some of the condition's accompanying contractions, In order to visualise the illness chord, this method entails making an

incision in the hand's palm.<sup>67</sup> After then, the contracture can be removed by severing the cord.<sup>67</sup> Although less intrusive than a closed fasciotomy, this treatment offers the advantage of directly visualising the diseased cord, which lowers the chance of injury to the hand's nerves. Dermafasciectomy is advised for the treatment of aggressive or recurring illness. In this lengthy procedure, the damaged fascia is removed together with the skin that covers it, and the skin is then closed using skin grafts.<sup>68,69</sup> The risk of illness recurrence is reduced with dermofasciectomy as opposed to fasci-ectomy alone. Therefore, this approach is occasionally advised for younger patients who have a history of aggressive disease recurrence, even if it necessitates longer postoperative rehabilitation. It is unknown what the long-term rate of recurrence will be. Six of the patients who finished the 8-year follow-up had suffered a return of the disease, according to a long-term study on collagenase injection for the treatment of developmental disorders. However, the majority of patients treated with collagenase demonstrated reduced joint contractures.<sup>79</sup> Collagenase injections in their current form are, at most, a convenient treatment because they do not address the collagen's cellular source. Finally, the long-term safety of injecting collagenase into hand regions that also contain normal tissue is questionable because this enzyme is not exclusive to the illness cord structure. It is unknown what makes up type I collagen in the palmar fascia and tendons. Even though DD frequently affects structural elements of the extracellular matrix (ECM), such as collagen, laminin, fibronectin, and elastin, proteases, such as those that affect a disintegrin and metalloprotease domain that contains protein 12, MMP-2, and MMP-9, proteo-glycans (particularly PRG4), and "matricellular" elements like periostin and tenascin C, have also been found to be affected.<sup>96, 97, and 99</sup> It has recently come to our attention that periostin stimulates the myofibroblast differentiation of DD cells while simultaneously causing the proliferation and apoptosis of phenotypically normal fibroblasts produced from the palmar fascia next to the DD cord. Certain ECM chemicals, such periostin, which cause DD cells and nearby fibroblasts to respond differently, may play distinct roles in the development and recurrence of DD and reflect. Therefore, the identification of these proteins may provide new treatment targets to stop the recurrence of DD.

## Conclusion

In conclusion, collagenase treatment for DD is still in its infancy

and has uncertain long-term consequences. However, it is not a cure. Despite the high likelihood of recurrence following this surgery, surgical excision continues to be the preferred course of treatment for the time being. New molecular targets have been identified as a result of recent developments in our knowledge of the molecular pathophysiology of this illness, which should pave the way for the development of more potent treatment options.

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