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## Dupuytren disease: Prevalence, treatment and outcome

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# Dupuytren disease

Prevalence, treatment and outcome

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FACULTY OF MEDICINE | LUND UNIVERSITY





Jesper Nordenskjöld is a resident in orthopedic surgery at Hässeholm-Kristianstad Hospitals in southern Sweden. His thesis explores Dupuytren disease, a disorder affecting the greatest of all tools- the hand.



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Prevalence, treatment and outcome

Jesper Nordenskjöld



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<b>Title and subtitle</b> Dupuytren disease: Prevalence, treatment and outcome		<b>Sponsoring organization</b> -	
<b>Abstract</b>			
<p><b>Purpose</b> To study the epidemiology of Dupuytren disease and evaluate treatment outcome of collagenase injections using a modified method.</p> <p><b>Patients and methods</b> <i>Paper I</i> is a register-based study. From the general population of Skåne region (1.3 million) in southern Sweden, we identified all residents aged <math>\geq 20</math> years who had been diagnosed with Dupuytren disease during a 16-year period and identified treatments associated with the diagnosis. <i>Papers II-V</i> are prospective cohort studies assessing patients with Dupuytren disease treated with collagenase injections using a modified method. Treatment indication was a palpable cord and an active extension deficit (AED) <math>\geq 20^\circ</math> in the metacarpophalangeal (MCP) and/or proximal interphalangeal (PIP) joint. In <i>Paper II</i>, 146 patients were evaluated for skin tear occurrence and short-term treatment outcome. In <i>Paper III</i>, 187 patients were divided into 3 groups, comparing collagenase injection-related pain with or without prior local anesthesia (LA) using the the visual analog scale (VAS). In <i>Paper IV</i>, 86 patients were evaluated 3 years after treatment with the proportion of joints that demonstrated contracture recurrence (AED worsening <math>\geq 20^\circ</math>) as the primary outcome. In <i>Paper V</i>, 157 patients were examined by 3 hand therapists, investigating possible examiner-related difference between AED and passive extension deficit (PED) measurements. <i>Paper VI</i> is an ongoing randomized controlled trial of surgical fasciectomy versus collagenase injection for recurrent Dupuytren disease.</p> <p><b>Results</b> The overall prevalence of doctor-diagnosed Dupuytren disease was 0.92%, peaking in men <math>\geq 70</math> years at 4.6%. 56% of diagnosed individuals underwent treatment. Skin tears, mostly minor, occurred in 40% of hands treated with collagenase injection. Greater severity of MCP joint contracture was a risk factor for skin tear. All skin tears healed with open-wound treatment, with no infections or surgical interventions required. Mean short-term contracture improvement in total AED was <math>55^\circ</math>. LA significantly reduced collagenase injection-related pain (mean VAS difference 2.1). At 3 years, complete correction (PED <math>0-5^\circ</math>) was observed in 3 of 4 MCP joints, but only in a third of PIP joints. Treatment of small finger PIP joint contractures, greater pretreatment contracture severity and previous surgical fasciectomy were significant predictors of recurrence. 70% of patients were satisfied with treatment and no adverse events were reported. The identity of the examiner was a significant determinant of the measured PED-AED difference.</p> <p><b>Conclusion</b> Dupuytren disease is a common cause of medical consultation. Collagenase injection is a safe and effective minimally-invasive treatment method, especially for MCP joint contractures. Skin tears commonly occur during the finger manipulation procedure, but the healing prognosis is excellent. LA significantly reduces collagenase injection-related pain. Measurement of PED may vary significantly between examiners. An ongoing randomized controlled trial will provide evidence regarding treatment of recurrent Dupuytren disease.</p>			
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Jesper Nordenskjöld



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*To my family, colleagues and patients*



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# List of publications

This dissertation is based on the following papers, referred to in the text by their Roman numerals. The original articles have been reprinted with the permission of the publishers.

I. **Nordenskjöld J**, Englund M, Zhou C, Atroshi I. Prevalence and incidence of doctor-diagnosed Dupuytren disease: a population-based study. *J Hand Surg Eur* Vol. 2017; 42 (7): 673-77.

II. Atroshi I, **Nordenskjöld J**, Lauritzson A, Ahlgren E, Waldau J, Waldén M. Collagenase treatment of Dupuytren's contracture using a modified injection method: a prospective cohort study of skin tears in 164 hands, including short-term outcome. *Acta Orthop*. 2015; 86 (3): 310-15.

II. **Nordenskjöld J**, Waldén M, Kjellin A, Franzén H, Atroshi I. Benefit of local anesthesia in reducing pain during collagenase injection for Dupuytren's contracture. *Plast Reconstr Surg*. 2017; 140 (3): 565-69.

IV. **Nordenskjöld J**, Lauritzson A, Åkesson A, Atroshi I. Collagenase injections for Dupuytren disease: 3-year treatment outcomes and predictors of recurrence in 89 hands. *Acta Orthop*. 2019; 90 (6): 517-22.

V. **Nordenskjöld J**, Brodén S, Atroshi I. Examiners' influence on the measured active and passive extension deficit in finger joints affected by Dupuytren disease *BMC Med Res Methodol*. 2018; 18 (1): 120.

VI. **Nordenskjöld J**, Lauritzson A, Waldén M, Kopylov P, Atroshi I. Surgical fasciectomy versus collagenase injections in treating recurrent Dupuytren disease: study protocol of a randomised controlled trial. *BMJ Open* 2019; 9: e024424.

# Abbreviations

AE	Adverse event
AED	Active extension deficit
CI	Confidence interval
CISSS	Cold intolerance symptom severity scale
EQ-5D	EuroQol 5-dimensions
LA	Local anesthesia
MCP	Metacarpophalangeal
OR	Odds ratio
PED	Passive extension deficit
PIP	Proximal interphalangeal
PROM	Patient-reported outcome measure
QuickDASH	Disabilities of the arm, shoulder and hand (11-item)
RR	Relative risk
SD	Standard deviation
VAS	Visual analog scale





# Chapter 1: Background

## 1.1 Introduction

Dupuytren disease is a common connective tissue disorder of the hand. The disease most often has a benign clinical presentation, with asymptomatic or occasionally tender soft tissue changes in the palm. However, as the disease progresses, cords and finger joint contractures develop, which may severely limit the function of the hand (Figure 1). Simple daily things, such as wearing gloves and shaking another person's hand, may be impossible for a patient affected by Dupuytren contracture.



Figure 1. Typical clinical presentation of Dupuytren contracture

Dupuytren disease was first described by the Swiss physician Felix Platter in 1614 (40), although the name of the disease was eponymously attributed to the French surgeon Baron Guillame Dupuytren (Figure 2) who lectured on the disease and demonstrated surgical treatment of contractures in 1831 (41). Although we have known about Dupuytren disease for hundreds of years, the etiology still remains unclear and we have no cure to offer our patients.



**Figure 2. Dupuytren statue at Hotel Dieu, Paris, France**

The foundation of this thesis is built on the lack of knowledge on Dupuytren disease. After reviewing current knowledge on Dupuytren disease, from a molecular level to practical treatment methods, research on a modern minimally-invasive treatment method will be presented, which is the main focus of this thesis.

## 1.2 The basic science

Although not the scope of this thesis, it is important to be familiar with the concepts of Dupuytren disease on the microscopic level in order to understand the clinical disorder and treatment methods. The main cell involved in the pathophysiology of Dupuytren disease is the myofibroblast (46). The myofibroblast originates from fibroblasts, a common connective tissue cell. Myofibroblasts have the ability to contract and produce collagen, which are key features in the formation of Dupuytren cords and finger contractures (19).

Three stages of progression have been described for Dupuytren disease (84):

1. *The proliferative stage.* Fibroblast proliferation leads to the development of nodules in the palm and fingers.
2. *The involutinal stage.* Fibroblast transformation into myofibroblasts producing predominantly type 3 collagen that organizes into cords that contract.
3. *The residual stage.* Myofibroblast regression leading to nodular disappearance with remaining hypocellular cords, with further contracture progression.

These stages are observed in the clinical setting, where the disease progresses from nodules to cords with contracture development as the disease end-stage. However, the time of progression varies widely among affected individuals (76).

What initiates the chain of progression into contracture development? Dupuytren disease has a strong genetic predisposition, but there is no simple genetic explanation and a multifactorial etiology has been suggested. From a genetic perspective, genome studies have identified several chromosomes containing multiple genes that may lead to and contribute to the severity of disease manifestation (97). The identified genes include mitochondrial genes (14), the MafB oncogene (81) and genes encoding proteins of the Wnt signaling pathway (17, 37), which are all involved in regulation of fibroblast proliferation.

Another important concept is the role of cytokines and growth factors (including transforming growth factor-beta, platelet-derived growth factor, and tumor necrosis factor). These mediators are secreted by immune cells of Dupuytren nodules (mainly lymphocytes and macrophages), and stimulate myofibroblast proliferation (7, 8, 136). Myofibroblast contraction and collagen production increase forces on the surrounding tissues promoting further matrix secretion by myofibroblasts (mechanotransduction), creating a disease-maintaining feedback loop (80).

The insights gained from preclinical research may open doors to research on new treatment methods that can target Dupuytren disease at an early stage and stop progression before contracture development (95). Dupuytren disease may also be an ideal model to study the pathophysiology of fibrosis in general (96).



## 1.3 Anatomy

The next step in the review is an anatomical perspective on Dupuytren disease. The disease affects the palmar and the digital fascia of the hand, presenting as nodules and cords. There is a dominant ulnar predilection, most commonly affecting the small and ring finger, and rarely involves the thumb and index finger. Describing the fascial structures is not an easy task since they blend together without well-defined borders. This review does not aim to be complete, but to review important anatomical concepts in order to understand the clinical presentation and treatment strategies for Dupuytren disease.

The palmar fascia is a continuation of the palmaris longus tendon at the level of the wrist (Figure 3). It is a triangular-shaped structure with a protective function of the underlying anatomical structures and skin stabilization. The palmar fascia is a three-dimensional structure containing longitudinal, transverse and vertical fibers (124). The palmar fascia diverges from the wrist in a distal direction as longitudinal pretendinous bands. The pretendinous bands attach superficially to the skin (at the level of the distal palmar crease and the proximal digital crease) and deep to the metacarpophalangeal (MCP) joint capsule and flexor tendon sheath. The intermediate fibers continue along the digit as two separate spiral bands to blend with a common fascia in the web space. The neurovascular bundle is located lateral to the pretendinous band. From the web space the fascia continues distally as lateral digital sheaths on either side of the finger, with the neurovascular bundle located medially. The lateral digital sheath connects with the volar Grayson ligament and dorsal Cleland ligament, which protects the neurovascular bundle. The transverse fibers of the palmar fascia include the superficial transverse palmar ligaments (deep to the pretendinous bands at the level of the distal palmar crease) and the natatory ligaments (at the level of the web spaces). The vertical fibers include the septae of Legueu and Juvara (vertical fibers connecting the palmar fascia to the metacarpal bones, deep transverse metacarpal ligaments and interosseous muscle fascia) and Grapow fibers (connecting the superficial palmar fascia to the skin). In the web space multiple fascial structures coalesce into a common fascia, the web space coalescence, including the spiral bands, the natatory ligament, the lateral digital sheath and the septae of Legueu and Juvara.

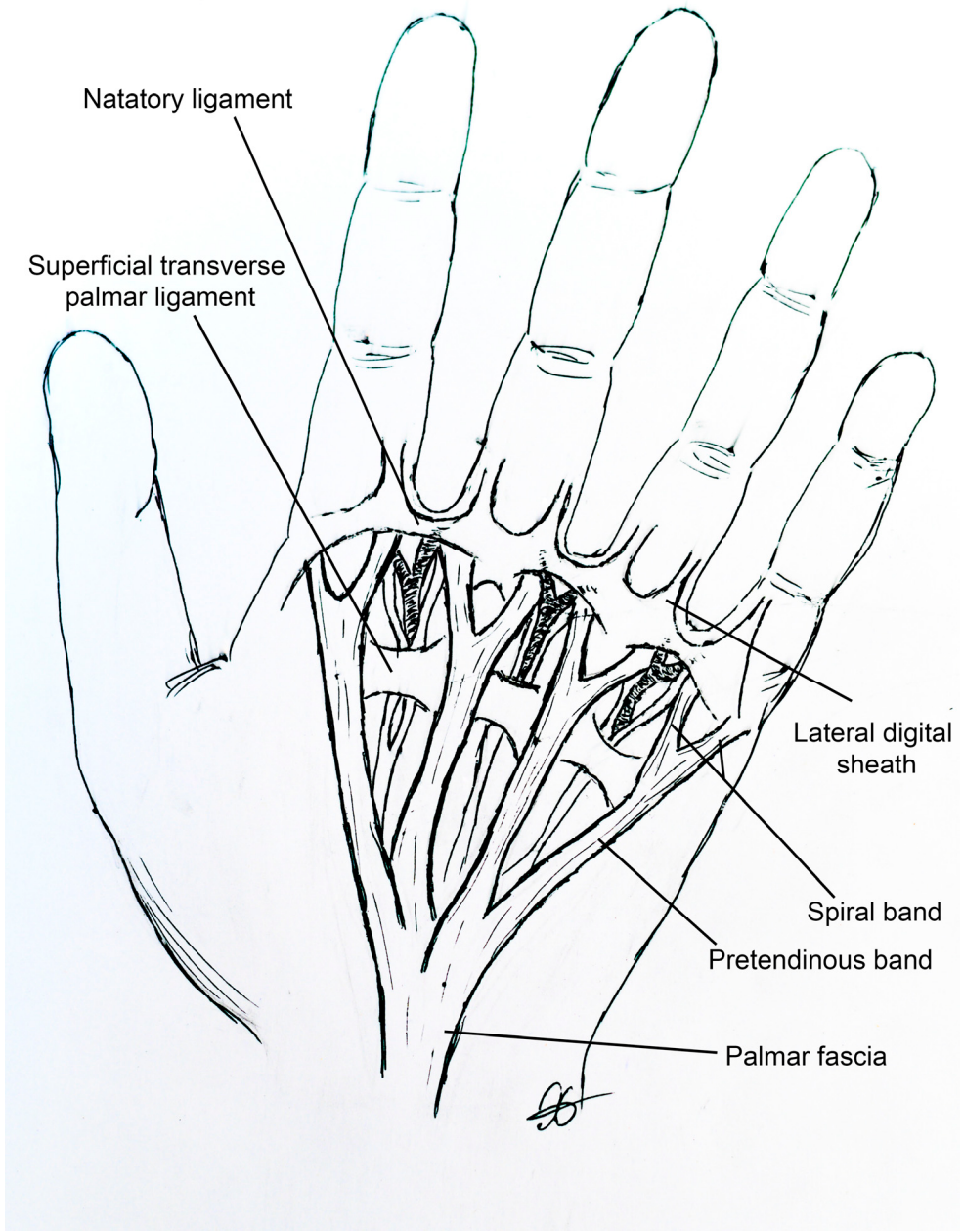


Figure 3. Normal anatomy of the palmar and digital fascia

In which of these anatomical structures does Dupuytren disease appear? Nodules appear between the skin and the superficial palmar fascia in random locations. Cords develop from normal fascial structures (Figure 4) in a predictable anatomical pattern (82). Cord formation usually begins in the pretendinous band giving rise to MCP joint contractures. The pretendinous cord may extend centrally (central cord) creating a proximal interphalangeal (PIP) joint contracture. PIP joint contractures may also arise from spiral bands (spiral cords) and lateral digital sheath (lateral cords), lying in close proximity to the neurovascular bundle with multiple anatomic variations (58). Isolated digital cords and retrovascular cords may also contribute to PIP joint contractures. Involvement of the transverse fibers may affect the web spaces and finger abduction.

Long-standing Dupuytren disease often leads to secondary joint-related contractures in PIP joints, due to tightness of the volar plate, accessory collateral ligaments, flexor tendon sheath and attenuation of the extensor tendon central band (129). This explains why PIP joints are more difficult to correct and have a higher tendency to recur after treatment.

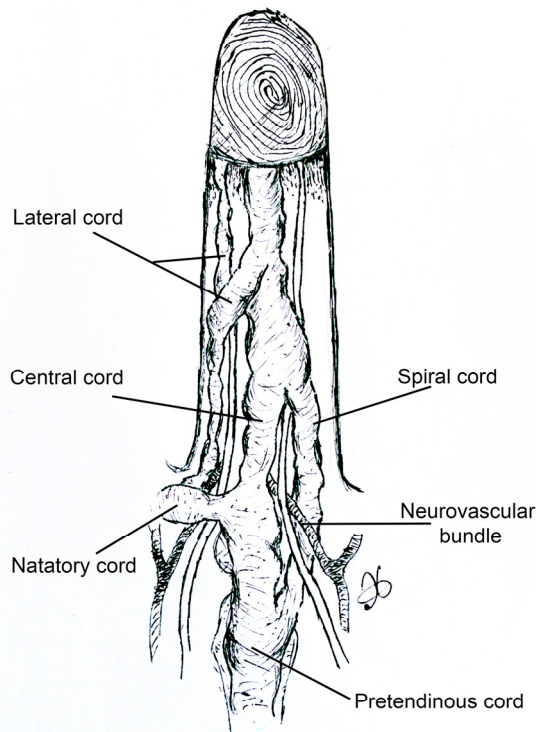


Figure 4. Pathological anatomy of the palmar and digital fascia

## 1.4 Epidemiology and risk factors

The review continues with an epidemiologic perspective. Dupuytren disease is a common disorder of the hand. The literature reports prevalence on all continents, however, the geographic distribution varies widely (61). The highest prevalence has been reported in the Caucasian population in western countries, especially in northern Europe (29, 54, 77). A systematic review on the prevalence of Dupuytren disease in western countries found prevalence rates of up to 32% (74). Hence, the disease is also called the Viking disease, but the disease seems to have existed before the age of the Vikings (90), and reports of Dupuytren disease prevalence in Asia and Africa cannot be explained only by migration (50, 141). Ethnic differences in prevalence can partly be explained by known genetic risk variants (105), but are also influenced by environmental factors (45).

When reviewing the epidemiology of Dupuytren disease it is vital to differentiate between the prevalence of disease and contractures. Although a high disease prevalence has been reported, the majority of affected individuals only have asymptomatic soft tissue changes in the palm causing no functional limitations. The prevalence of contractures is much lower (29, 54, 77). Lanting et al. examined 344 hands affected by Dupuytren disease, observing contractures in 15% of fingers (75). The literature addressing the extent to which individuals actually seek medical consultation and undergo treatment for Dupuytren disease is scarce.

Several risk factors have been associated with Dupuytren disease (Table 1). From the knowledge of genetic and environmental risk factors, the concept of the Dupuytren diathesis has evolved. The Dupuytren diathesis describes a constitution of features that predispose an individual to Dupuytren disease, with an aggressive disease course and high recurrence rate after intervention. Originally described by Hueston in 1963 (67), it was revised by Hindocha in 2006 (62). The Dupuytren diathesis includes bilateral disease, positive family history, young age at onset (<50 years), male gender, ethnicity and ectopic disease. The latter includes knuckle pads (thickened nodules dorsal on PIP joints), Peyronie disease (penile induration) and Ledderhose disease (plantar fibromatosis).

**Table 1. Risk factors associated with Dupuytren disease**

---

Heredity	A strong heritability (approximately 80%) observed in twin pairs (78). Positive family history associated with earlier onset and more severe disease manifestation (36, 60).
Increasing age	A meta-analysis estimated a prevalence of 12%, 21% and 29% at age 55, 65 and 75 years, respectively, in western countries (74).
Male sex	Mean male-to-female ratio approximately 6:1 in a systematic review (61), although lower (1.2:1) in a recent prevalence study in the Netherlands (77). Men younger age at surgical intervention (140).
Hand trauma	Including previous injury, surgery, manual labour, repetitive sports activities (18, 23, 54, 77).
Adhesive capsulitis	Frozen shoulder has a strong association with Dupuytren disease (relative risk 8), and also many similarities in pathogenesis (122).
Smoking, alcohol	Smoking has been associated with Dupuytren disease (24, 54), whereas alcohol as a risk factor is more controversial (59). A combination of smoking and alcohol may have a synergistic effect (52).
Diabetes mellitus, liver disease, epilepsy	A recent meta-analysis have demonstrated an association (odds ratios 2.8 to 3.1) between Dupuytren disease and diabetes mellitus, liver disease and epilepsy (21).
Hypercholesterolemia	Patients with Dupuytren disease have been shown to have higher fasting cholesterol and triglyceride levels than controls (113).

---

## 1.5 Treatment

The review continues with a more practical approach to Dupuytren disease; treatment options for patients seeking medical advice for debilitating contractures. An optimal treatment method for Dupuytren disease would have the following characteristics:

1. Effective in reducing contractures
2. Safe
3. Easy to learn and perform
4. Rapid recovery after intervention
5. Cost-effective

No cure exists at present for Dupuytren disease, and none of the available treatment methods can be considered optimal.

Treatment of Dupuytren disease can be classified into early disease control (non-surgical treatment methods) and contracture treatment (open surgery, minimally-invasive treatment methods). Indication for contracture treatment is commonly defined as an extension deficit of  $\geq 20^\circ$  in the MCP and/or PIP joint (65) or a total finger extension deficit of  $\geq 30^\circ$  (132). Hueston introduced a simple table top test, positive when the patient is unable to put the affected finger flat on a table, as an indication for treatment (64). Open surgery (surgical fasciectomy) is the most commonly used treatment method for Dupuytren disease (31, 51, 83), although minimally-invasive treatment methods (including needle fasciotomy and collagenase injection) have gained in popularity in recent years.

How is treatment efficacy assessed? Range of motion is almost always used as the primary outcome measure in Dupuytren disease research, and more specifically the extension deficit in a finger with joint contractures (12). Extension deficit can be measured either as passive (PED) or active (AED), separately for each joint or as total extension deficit. Commonly used secondary outcomes include adverse events (AEs), patient-reported outcome measures (PROMs) and treatment cost.

### **Non-surgical treatment**

Non-surgical treatment methods aim to control early Dupuytren disease and prevent contracture development. Available non-surgical treatment methods are:

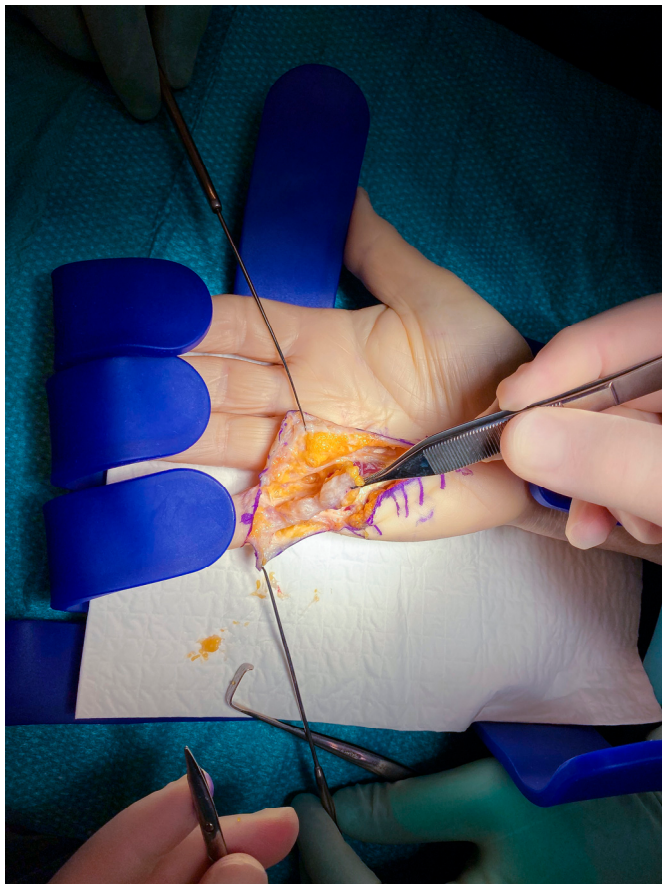
1. Low-dose radiotherapy.
2. Pharmacologic treatment including steroids (local injection, topical and oral) and vitamin E.
3. Physiotherapy including splinting, ultrasound, frictional massage and heat treatment with joint stretching.

These methods have the advantage of being safe (with the exception of radiotherapy toxicity) and easy to perform with a rapid hand recovery. The disadvantage is the lack of evidence regarding treatment efficacy, highlighted by recent systematic reviews (11, 138), and these methods are therefore used rarely nowadays.

### **Open surgery**

Surgical fasciectomy corrects contractures by excision of pathological fascia. The indication for surgical fasciectomy is treatment of both MCP and PIP joint contractures, including severe and recurrent contractures (32). The procedure is performed in the operating room in general or regional anesthesia with a tourniquet to allow clear visualization.

There are several variants of surgical fasciectomy techniques. Segmental fasciectomy is performed using multiple small incisions to remove sections of the cord (93). Limited fasciectomy (63), the most commonly used variant, involves more extensive fascia excision (Figure 5). Several skin incision types can be used, including zig-zag incision and midline longitudinal incision closed by Z-plasties (32). Careful dissection is important to avoid injuries to the neurovascular bundles. For severe or recurrent disease the procedure can be extended to dermofasciectomy, removing all pathological tissue contributing to the contracture including skin (2). Skin defects may be covered by a full-thickness skin graft or left to heal by secondary intention (88). Surgical fasciectomy can be combined with additional procedures addressing persistent secondary PIP joint contracture, such as capsulotomy and collateral ligament release.



**Figure 5. Limited fasciectomy for recurrent PIP joint contracture of the small finger using a zig-zag incision**

Postoperative care includes wound management, hand therapy and the use of a night-time splint, although the latter lacks support in the literature (66, 72, 79, 112).

According to available evidence, surgical fasciectomy is the most effective treatment method for Dupuytren disease with the lowest reported recurrence rate (33, 130, 133). One disadvantage is a substantial risk of severe AEs including infection and skin necrosis, neurovascular injury, joint stiffness and complex regional pain syndrome (30, 32, 100). The risk of AEs increases with contracture severity and in recurrence treatment (33). Furthermore, complete hand recovery takes weeks or even months after surgery (44). The procedure requires surgical experience and the resources of the operating room, increasing treatment-related cost (51).

### **Needle fasciotomy**

Needle fasciotomy involves percutaneous division of Dupuytren cords using needles (10). The main indication for needle fasciotomy is mild to moderate MCP joint contractures, although some authors also advocate its use in PIP joint contractures (42). Needle fasciotomy is a minimally-invasive procedure that can be performed in an outpatient setting during a single visit.

Entry portals (2-10) are marked along the palpable cord (Figure 6). Local anesthesia (LA) is infiltrated subdermally at the portals. A needle is inserted perpendicular to the cord that is then divided by clearing, perforating and sweeping movements (38). Care is taken not to injure the neurovascular bundle and flexor tendons. This requires direct feedback from the patient, by reporting the occurrence of tingling sensation or sharp pain. Needle fasciotomy can be combined with steroid injections, which may improve the outcome up to 24 months (91). A technique using adjunctive lipofilling has also been described (68).





**Figure 6. Needle fasciotomy entry portals marked on a pretendinous cord**

Postoperative care is simple, including wound management if skin tears occurred and simple hand exercises. Specific hand therapy or splinting is not required and rarely used (127).

Advantages of needle fasciotomy includes low incidence of AEs and rapid recovery of hand function (94, 132). Treating MCP joint contractures is relatively easy, whereas PIP joint treatment requires greater experience. Furthermore, it is a low-cost treatment method that does not require the resources of the operating room (13). Disadvantages include the high long-term recurrence rate and limitations in the treatment of severe contractures and PIP joints (101, 133).

### **Collagenase injection**

Collagenase clostridium histolyticum is an enzyme that lyses collagen (85). Targeting the pathological palmar fascia of Dupuytren disease, collagenase injection became available as the first pharmacological treatment method for

contractures in 2010 (5). The indication for collagenase injection includes treatment of both MCP and PIP joint contractures (6, 65). Collagenase injection is used in an outpatient setting, but requires 2 visits (injection and finger manipulation).

According to the standard method, treatment comprises injection of collagenase (0.58 mg) directly into the cord, followed by finger manipulation to disrupt the cord 24 hours after injection (Figure 7). In the initial multicenter trial, the manipulation procedure was performed without LA, to avoid a potential confounding factor (65). Furthermore, joints were treated separately with a minimum of 30-day interval. The procedure has since then been modified; the use of LA before manipulation is now considered standard practice (86), and multiple joints can be treated simultaneously using higher doses without increasing the number of AEs (26, 49, 53). The manipulation procedure can also be delayed up to 4 days without loss of efficacy (70).



**Figure 7. Collagenase injection in the outpatient clinic**

Postinjection care is similar to that of needle fasciotomy, including potential skin tear management and simple hand exercises. Night-time splinting was used in the

original trial for 4 months, although there is no evidence to support its use. Specific hand therapy is rarely required.

Advantages of collagenase injection are treatment of multiple joint contractures in one session in a minimally-invasive manner, including the PIP joint. The procedure is relatively easy to perform. There is a low incidence of severe AEs, although mild transient AEs (swelling, hematoma, skin tears, pruritus and axillary pain) are common (73, 114). No nerve injuries have been reported, and flexor tendon rupture and vascular complications are extremely rare (102, 123). Furthermore, the procedure can be performed at the outpatient clinic, and is cost-effective in comparison to surgical fasciectomy (4, 117), but is more expensive than needle fasciotomy (25). A disadvantage is the long-term recurrence rate using the standard technique (98, 139), but this has to be further investigated with the evolution of treatment protocols.

## **Comparison of treatment methods**

Comparison between studies on treatment outcome is difficult. Dupuytren disease covers a large spectrum of disease severity and patient selection varies widely among studies, from studies treating nodules (27) and isolated MCP joint contractures (89, 125), to studies treating all contractures (98, 133). Definitions of recurrence and clinically relevant contracture reduction vary among studies (137). The outcome measures vary between studies, and in some studies the treating surgeon measures the outcome, raising the question of bias (103). Another issue is the length of follow-up needed to properly assess recurrence, and few studies report outcomes at 3 years and longer. Currently, there is insufficient evidence available to show the relative superiority of different surgical procedures, highlighted by a recent Cochrane review (107). Globally, widespread differences are observed in the management of Dupuytren disease, likely due to the lack of clear evidence and guidelines (92).

There are, however, a few randomized controlled trials comparing treatment methods for Dupuytren disease (Tables 2-4):

### *Limited fasciectomy versus dermofasciectomy*

Ullah et al. compared limited fasciectomy versus dermofasciectomy using a skin graft in 79 randomized patients with PIP joint contractures of  $>30^\circ$  (130). At 3 years, the study found no between-group difference in terms of recurrence (total 12.2%), range of motion, grip strength and AEs.

**Table 2. Limited fasciectomy versus dermofasciectomy**

Authors	n	Treatment	Inclusion criteria	Follow-up	Recurrence definition	Primary outcome	Results
Ullah et al. 2009 (130)	79	LF vs DF	PIP contracture >30°	3 years	Not defined	Recurrence	LF 10.9% vs DF 13.6% (p=0.6)

DF; dermofasciectomy, LF; limited fasciectomy, PIP; proximal interphalangeal.

### *Limited fasciectomy versus needle fasciotomy*

Van Rijssen et al. compared limited fasciectomy versus needle fasciotomy in 111 patients treated for contractures with a total PED  $\geq 30^\circ$  (132, 133). At 6 weeks, better contracture reduction was observed in the limited fasciectomy group, but fewer AEs and faster hand recovery were seen in the needle fasciotomy group. At 5 years, 93 of the 111 randomized patients were assessed. Recurrence (defined as an increase in total PED  $\geq 30^\circ$  from 6 weeks after treatment), was observed in 9 of 43 hands (20.9%) in the limited fasciectomy group and 45 of 53 hands (84.9%) in the needle fasciotomy group.

Selles et al. compared limited fasciectomy versus needle fasciotomy with lipofilling (118). No difference in outcome was found at 1 year (68). At 5 years, assessing 52 of 80 randomized patients, significantly higher recurrence in the needle fasciotomy group (32% in the limited fasciectomy group and 77% in the needle fasciotomy with lipofilling group, according to Van Rijssen's definition). No randomized controlled trial has compared needle fasciotomy with or without lipofilling.

**Table 3. Limited fasciectomy versus needle fasciotomy**

Authors	n	Treatment	Inclusion criteria	Follow-up	Recurrence definition	Primary outcome	Results
Van Rijssen et al. 2012 (133)	93	LF vs NF	TPED $\geq 30^\circ$	5 years	TPED $\geq 30^\circ$	Recurrence	LF 20.9% vs NF 84.9% (p<0.001)
Selles et al. 2018 (118)	52	LF vs PALF	FC MCP $\geq 20^\circ$ and/or PIP $\geq 30^\circ$	5 years	ED >20° or secondary procedure	Recurrence	LF 39% vs PALF 74% (p=0.002)

ED; extension deficit, FC; flexion contracture, LF; limited fasciectomy, MCP; metacarpophalangeal, NF; needle fasciotomy, PALF; percutaneous aponeurotomy with lipofilling, PIP; proximal interphalangeal, TPED; total passive extension deficit.

### *Collagenase injection versus needle fasciotomy*

Scherman et al. compared collagenase injection (using the standard method) versus needle fasciotomy in patients with predominantly MCP joint contractures (115). Assessing 76 of 93 randomized patients at 3 years, no difference in recurrence rate was observed. 11 patients were retreated in the needle fasciotomy group compared to 4 patients in the collagenase group, but this was not a significant difference (p=0.09). No between-group differences were observed in PROMs.

Strömberg et al. compared collagenase injection (standard method) versus needle fasciotomy for isolated MCP joint contractures (126). Assessing 152 of 156 randomized patients at 2 years, complete correction (extension deficit  $<5^\circ$ ) was observed in 76% in the collagenase group and 79% in the needle fasciotomy group. No differences were observed in the secondary outcome measures including recurrence rate, range of motion and PROMs.

Skov et al. compared collagenase injection (standard method) versus needle fasciotomy for primary isolated PIP joint contractures (120). Assessing 43 of 50 randomized patients at 2 years, clinical improvement (contracture reduction  $\geq 50\%$ ) was maintained in 2 of 24 PIP joints (8%) in the collagenase group and in 6 of 19 PIP joints (32%) in the needle fasciotomy group.

In all these trials, no patients suffered from any severe AEs. More AEs, although mild and transient, were observed in patients treated with collagenase injection.

**Table 4. Collagenase injection versus needle fasciotomy**

Authors	n	Treatment	Inclusion criteria	Follow-up	Recurrence definition	Primary outcome	Results
Scherman et al. 2018 (115)	76	CCH vs NF	TPED 30-135° (PIP $<60^\circ$ )	3 years	TPED $\geq 30^\circ$ or retreatment	Recurrence	CCH 33.3% vs NF 42.5% (p=0.65)
Strömberg et al. 2018 (126)	152	CCH vs NF	ED MCP $\geq 20^\circ$	2 years	ED $\geq 20^\circ$	Complete correction (ED $<5^\circ$ )	CCH 76% vs NF 79% (p=0.7)
Skov et al. 2017 (120)	43	CCH vs NF	PED PIP $\geq 20^\circ$	2 years	PED $\geq 20^\circ$	Contracture reduction $\geq 50\%$	CCH 8% vs NF 32% (p=0.05)

CCH; collagenase clostridium histolyticum, ED; extension deficit, MCP; metacarpophalangeal, NF; needle fasciotomy, PED; passive extension deficit, PIP; proximal interphalangeal, TPED; total passive extension deficit.

### *Collagenase injection versus limited fasciectomy*

No randomized controlled trials comparing collagenase injection versus limited fasciectomy are published, although several trials are ongoing (104).

## **Treatment of recurrence**

Currently, no cure is available for Dupuytren disease, and all treatment methods are associated with recurrence. Traditionally, surgical fasciectomy has been the standard treatment method for recurrence, with the advantage of the possibility to release periarticular structures contributing to the recurrent contracture (71). Surgery for recurrence is, however, technically more challenging than the index surgery due to scar formation with a higher incidence of severe AEs (30). The minimally-invasive treatment methods can be used for recurrence with a well-

defined palpable cord, with good short-term results (15, 134). No randomized controlled trials have compared treatment methods for recurrence.

In severe recurrence, usually in the small finger PIP joint with secondary joint contracture and no palpable cord, salvage procedures, such as PIP joint fusion and amputation, may be considered (Figure 8) (28, 71). Other salvage procedures have been reported with satisfactory outcome, such as middle phalangeal resection (39).



**Figure 8. Amputation of the small finger as a salvage procedure for severe recurrence**



# Chapter 2: Aims

## 2.1 General aims of the thesis

The general aim of this thesis is to improve knowledge on Dupuytren disease with regard to epidemiology, outcome measures and treatment outcome. The main scope is on the minimally-invasive treatment method collagenase injection, assessing efficacy and safety.

## 2.2 Specific aims of the included studies

### *Paper I*

To investigate the prevalence and incidence of doctor-diagnosed Dupuytren disease and associated treatment methods.

### *Paper II*

To assess short-term treatment efficacy and incidence of skin tears after treatment with collagenase injection using a modified method.

### *Paper III*

To study the pain aspect of collagenase treatment and investigate the benefit of local anesthesia in reducing pain during injection.

### *Paper IV*

To assess the mid-term (3-year) treatment outcome of collagenase injection, including predictors of recurrence and patient dissatisfaction.

### *Paper V*

To assess the examiner's influence on two common outcome measures in Dupuytren research, active and passive extension deficit.

### *Paper VI*

To compare effectiveness of surgical fasciectomy versus collagenase injection in treating recurrent Dupuytren disease.





# Chapter 3: Patients and methods

## 3.1 Study population and methods

*Paper I* is a register-based study. The study population is the population of Skåne region in southern Sweden (1.3 million inhabitants). Using the Skåne Healthcare Register, we identified all residents aged  $\geq 20$  years (on December 31, 2013) who had consulted a medical doctor during a 16-year period (1998-2013) and were given the diagnosis Dupuytren disease (International Classification of Diseases, 10<sup>th</sup> revision, code M720). We excluded individuals who had relocated from the study region or were deceased by December 31, 2013. We also determined the type of healthcare facility where the diagnosis was recorded (primary, secondary and tertiary level) and identified treatments given in association with the diagnosis, using the Swedish Classification of Healthcare Interventions codes ((NDM19 (fasciectomy), NDM09 (fasciotomy), TND11 (therapeutic injection), DNO10 (collagenase injection), NDQ15 (total finger amputation), NDQ16 (partial finger amputation), NDG46 (interphalangeal joint arthrodesis)). The specific intervention code for collagenase injection was first introduced in January 2013.

*Papers II-V* are prospective cohort studies. The study setting is one orthopedic department (Hässleholm-Kristianstad Hospitals) in southern Sweden, with the addition of another orthopedic department (Ängelholm Hospital) in *Paper III*. The main study center is the only department treating Dupuytren disease in a region with approximately 300,000 inhabitants, and no patients are referred to other centers for treatment. The treatment indication at the department is a palpable Dupuytren cord and AED  $\geq 20^\circ$  in the MCP and/or PIP joint. The studies enrolled patients who were referred from primary care, or who directly sought care for Dupuytren disease, and were scheduled for treatment with collagenase injection. Collagenase was introduced at the study center in September 2011, and is the first-line treatment method for primary Dupuytren disease. The number of surgical fasciectomies performed during the study period are presented as supplemental data (Appendix). Needle fasciotomy was not performed at the study center during the study period.

For *Papers II-V*, patients were recruited from November 2012 through December 2015 (Figure 9). *Paper IV* is a follow-up study of *Paper II* assessing treatment outcome at 3 years, including a part of the original cohort. Finally, 32 patients were included in both *Papers II* and *III* (enrolled from November 6 to November 27, 2013) and 18 patients were included in both *Papers III* and *V* (enrolled from August 12, 2014 to September 9, 2014). In *Paper III*, patients from the second study center (Ängelholm Hospital) were enrolled from September through November 2015. Baseline characteristics for patients included in *Papers II-V* were similar (Table 5).

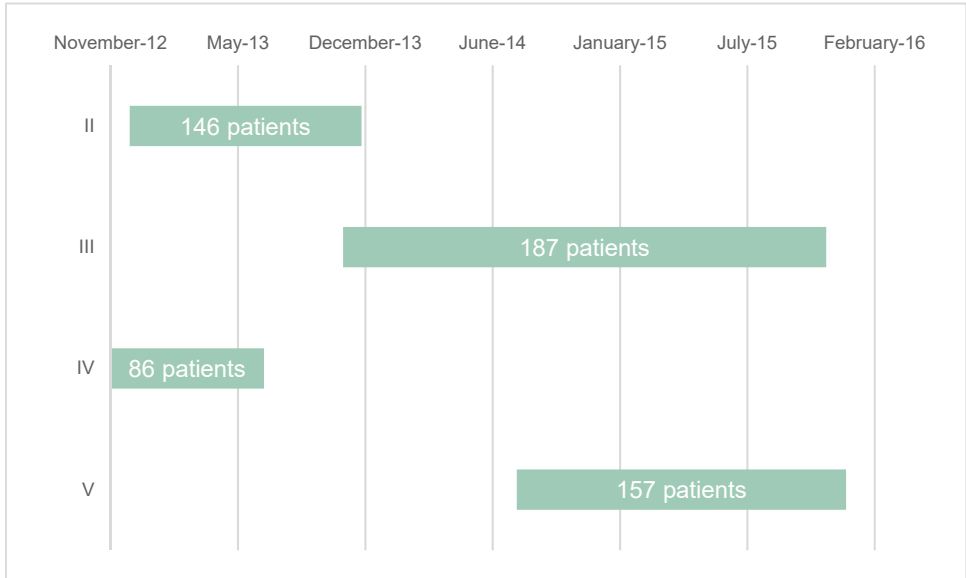


Figure 9. Timeline of study populations (*Papers II-V*)

**Table 5. Baseline characteristics (Papers II-V)**

		<i>Paper II</i>	<i>Paper III</i>	<i>Paper IV</i>	<i>Paper V</i>
Patients, n		146	187	86	157
Age, mean (SD)		70 (9)	69 (9)	72 (8)	70 (8)
Sex, n (%)	Women	29 (20)	37 (20)	22 (26)	30 (19)
	Men	117 (80)	150 (80)	64 (74)	127 (81)
Finger, n	Small	111	105	56	165
	Ring	89	65	49	106
	Middle	38	16	17	18
	Index	5	0	3	2
	Thumb	3	1	1	0
Previous treatment, n (fingers)	LF	23	NA	15	NA
	NF	3	NA	0	NA
No. of injections (per patient)	1	124	158	79	NA
	2	22	29	7	NA
Injection-extension interval	1 day	49	28*	30	NA
	2 days	97	133*	56	NA
AED, mean (SD) degrees	Total	79 (34)	80 (36)*	75 (39)	NA
	MCP	43 (27)	40 (29)*	44 (25)	49 (22)
	PIP	36 (29)	39 (26)*	31 (29)	41 (20)

NA; not applicable (not investigated in the study), \*; data from main study center (no data available for 26 patients from study center 2), AED; active extension deficit (Total= MCP+PIP), LF; limited fasciectomy, MCP; metacarpophalangeal, NF; needle fasciotomy, PIP; proximal interphalangeal, SD; standard deviation.

*Paper VI* is a protocol for a parallel-group single-center randomized controlled trial. Using the same referral procedures as in *Papers II-V*, patients with recurrent Dupuytren disease are routinely appointed to and examined by specialists in hand surgery or orthopedics and screened for eligibility according to defined inclusion and exclusion criteria (Table 6). Baseline demographic data are documented for all enrolled patients (including family history, smoking, alcohol consumption, diabetes mellitus, bilateral disease, type of work). Patients are randomized to either surgical fasciectomy or collagenase injections according to a computer-generated randomization list (in blocks of 4 or 6). The randomization ratio is 1:1 and stratified according to previous treatment (surgical fasciectomy or collagenase injection) and affected finger (small finger affected or small finger not affected). Patients randomized to surgical fasciectomy or collagenase injection are put on the department's waiting list according to standard routine, and will undergo surgery or injection treatment within 2 months.

**Table 6. Inclusion and exclusion criteria (Paper VI)**

Inclusion criteria	Exclusion criteria
Patient (age $\geq 18$ years) seeking treatment for Dupuytren disease recurrence in at least 1 finger (small, ring or middle finger)	Medical comorbidities constituting absolute contraindication for surgical fasciectomy or collagenase injection
PED $\geq 30^\circ$ in the MCP and/or PIP joint in a finger previously treated with surgical fasciectomy or collagenase injection	Signs of nerve or vascular injury in the affected finger
Palpable cord in the palm and/or affected fingers deemed to be the cause of the recurrent contracture	Complications after the previous treatment (infection, neurovascular injury, complex regional pain syndrome)
No surgery or collagenase injection in the study hand in the past 12 months	Severe osteoarthritis involving the MCP or PIP joint in the affected finger
	Previous trauma or other surgery involving the affected finger
	More than 2 previous surgical fasciectomies or collagenase treatments in the affected finger
	Previous treatment with both surgical fasciectomy and collagenase in the affected finger
	The examining surgeon deems further surgical fasciectomy to be inappropriate or potentially associated with very high complication risk, for example in severe contracture and/or scarring after previous surgery, and consider salvage procedures as the more appropriate treatment

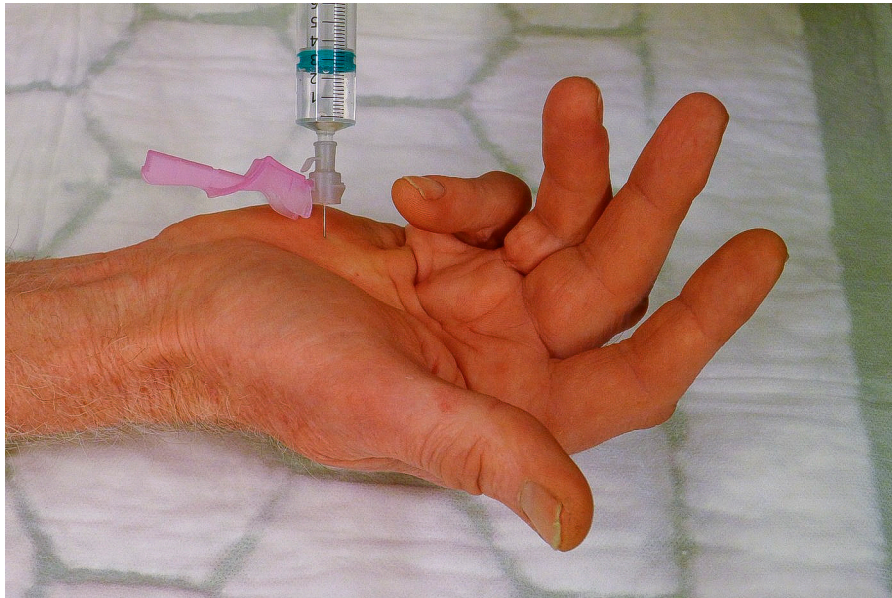
MCP; metacarpophalangeal, PED; passive extension deficit, PIP; proximal interphalangeal.

## 3.2 Interventions

### Collagenase injection

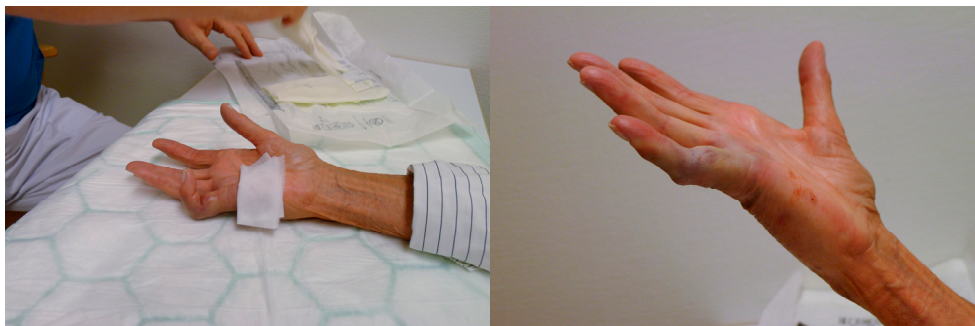
Collagenase treatment is provided in an outpatient setting by a single hand surgeon. In the clinical studies (*Papers II-VI*) we have used a modified treatment regime which differs from the originally described method:

1. The use of a higher dose. After reconstituting collagenase with 0.39 ml of diluent, all reconstituted collagenase (approximately 0.80 mg) is injected into the cord. If patients are treated for contractures in multiple joints and fingers, 2 vials may be used.
2. Collagenase is injected into multiple spots in the cord (usually 3-4 spots), from the palmar crease to the PIP joint, depending on cord dissemination.
3. LA (10 mg/ml mepivacaine buffered with sodium bicarbonate) is administered before the manipulation procedure as a digital nerve block in the proximal palm to enable an optimal painless contracture reduction (Figure 10).



**Figure 10. Local anesthesia administered as a nerve block in the proximal palm**

Following collagenase injection an assistant nurse applies a soft dressing and the patient is instructed to avoid heavy use of the hand. The patient returns to the outpatient clinic after 1 or 2 days (as the schedule permits) for the manipulation procedure. The surgeon injects LA and after about 20 minutes performs finger manipulation by applying pressure with the thumb along the cord to disrupt it and then manipulating the MCP and PIP joints into maximum possible extension (Figure 11).



**Figure 11. Before and after the finger manipulation procedure**

Immediately after finger manipulation, a hand therapist applies a static splint (mostly custom-made) with fingers in maximal possible extension and gives instructions on edema management and range of motion exercises. The patients are instructed to use the splint at night for 8 weeks, with adjustment 1 week after treatment. All skin tears are managed conservatively using standard wound dressing. Follow-up visits to the assistant nurse or a primary care nurse are scheduled depending on skin tear severity. In case of incomplete contracture reduction patients are offered a second injection (minimum 30 days interval).

In *Paper III*, we evaluated the potential benefit of LA in reducing the collagenase injection-related pain. Patients were enrolled into 3 groups:

1. Collagenase injection (modified method) without LA (78 patients).
2. Collagenase injection (modified method) with LA (83 patients).
3. Collagenase injection (standard method) without LA (26 patients).

Patients in groups 1 and 2 were enrolled at the main study center by alternating treatment sessions. Patients in group 3 were enrolled at the second study center (Ängelholm Hospital) with the sole purpose of comparing pain scores between the modified and the standard treatment method. The LA was administered using the same technique as before the manipulation procedure.

## **Surgical fasciectomy**

Surgical fasciectomy is performed in *Paper VI* according to standard practice by a single hand surgeon with extensive experience in surgery for Dupuytren disease. The surgeon is allowed to choose the type of anesthesia (general or axillary block) in consultation with the anesthetist, type of incision, the extent of the fasciectomy (limited fasciectomy or dermofasciectomy), whether to perform additional procedures (such as PIP joint capsulotomy), and postoperative care (such as type and duration of any splinting and frequency of dressing change). The patients will return to the outpatient department for suture removal approximately 2 weeks postoperatively. The treating hand occupational therapist (not involved in the trial) will decide the frequency of treatment visits, depending on the status of the treated hand (consulting the treating surgeon when necessary).

### 3.3 Outcome measurements and follow-up procedures

All measurements in the thesis are performed independently of the treating surgeons. Outcome measurements used in the thesis include:

1. Physical examination.
2. AEs.
3. PROMs.
4. Treatment cost.

Study-specific outcome measurements and follow-up procedures for *Paper VI* are summarized below (Table 6-7).

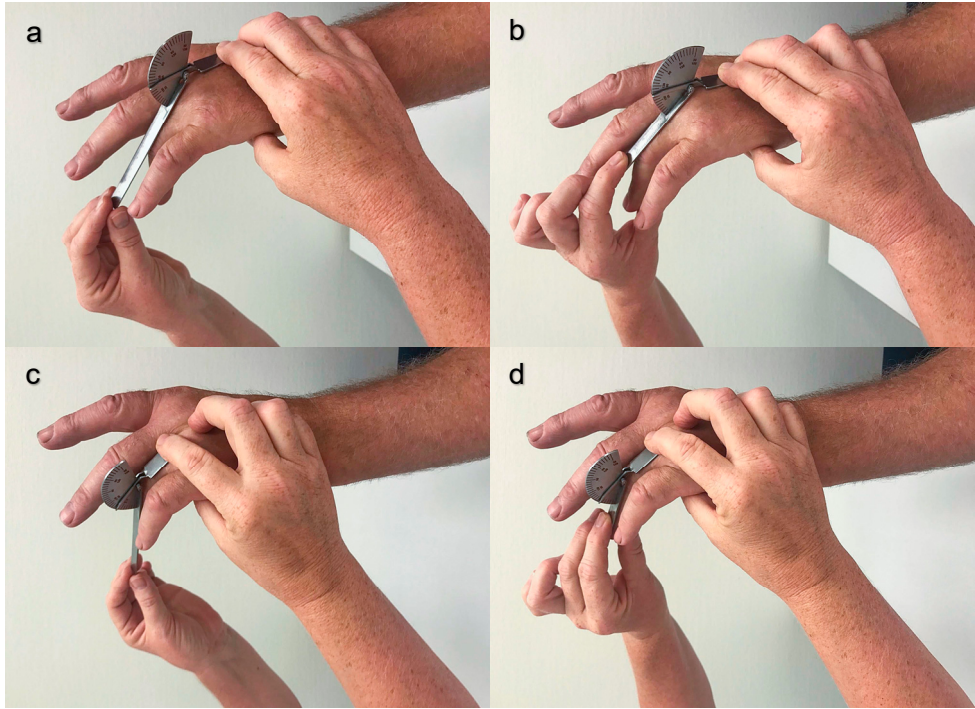
#### **Physical examination**

In the treatment outcome studies (*Papers II, IV and VI*) we have used the extension deficit as the primary outcome measure. In *Paper II* we only measured AED, but we added measurements of PED in *Papers IV and VI* to enable comparison with other studies that have used PED exclusively. *Paper V* examines the measured AED and PED difference between three experienced hand therapists.

The physical examinations were performed by hand therapists. Measurements were performed before treatment and at follow-up evaluations, according to a standardized protocol. A hand-held metal goniometer was used for measurements of extension deficits. MCP and PIP joints were measured separately (Figure 12). Hyperextension was recorded as 0°. During measurement the patient has the elbow in a flexed position resting on the examination table and the forearm and wrist in neutral position. The examiner asks the patient to actively extend the fingers as much as possible and measures AED of each joint. Measurement of AED in the PIP joint is performed with the MCP joint actively extended. After measuring AED, the examiner measures PED by applying pressure on the finger to extend the joints until resistance. Measurement of PED in the PIP joint is performed with the MCP joint in maximum possible active extension, to standardize the phenomenon of dynamism (109).

In *Paper VI*, all patients enrolled in the trial are examined by one of two trial hand therapists (not involved in the post-treatment care of the patients). Patients will wear a thin glove on the treated hand during the follow-up examination by the trial hand therapist to conceal treatment allocation. In *Paper VI* grip strength measurement (JAMAR dynamometer) and Semmes-Weinstein monofilament test of sensation are also performed.





**Figure 12. AED and PED measurements of MCP and PIP joints separately (a; AED in MCP joint, b; PED in MCP joint, c; AED in PIP joint, d; PED in PIP joint)**

## **Adverse events**

AEs are documented during interventions (by the surgeon) and at all follow-up evaluations (*Papers II, III, IV, VI*), independently of the treating surgeon, using a standardized protocol. Severe AEs include nerve injury (irreversible), vascular injury, tendon rupture, complex regional pain syndrome, deep infection, severe loss of flexion in the treated finger, or any complication requiring surgical intervention or hospital admission.

In *Paper II*, full-thickness skin tears of any size were documented by the assisting nurse. Skin tear's location and largest diameter were recorded (using a surgical ruler). A second nurse visit was routinely scheduled (within 2 to 5 days), with additional visits depending on skin tear status. A telephone follow-up was scheduled by the nurse 2 to 4 weeks after treatment to record the time to wound healing.

Common mild transient AEs related to collagenase injection such as swelling and hematoma have not been documented in the thesis.

## **Patient-reported outcome measures**

In *Paper III*, the assisting nurse asked the patients to rate the intensity of injection-related pain on a visual analog scale (VAS), ranging from 0 (no pain) to 100 (worst pain). In the same manner, the nurse asked the patient to rate the injection-to-manipulation interval pain, when returning for the manipulation procedure 1 to 2 days later.

In *Paper VI*, patients rated their satisfaction with treatment on a 4-point scale (1 very satisfied, 2 satisfied, 3 neutral, and 4 dissatisfied).

In *Paper VI*, multiple PROMs are used, including:

1. The 11-item disabilities of the arm, shoulder and hand (QuickDASH) questionnaire, a measure of activity limitations related to upper extremity disorders, with a total score range from 0 (best) to 100 (worst) (55).
2. The EuroQol 5-dimensions (EQ-5D), a 5-item measure of health status and quality of life, with a score range from -0.594 (worst) to 1.0 (perfect health) (35).
3. The cold intolerance symptom severity scale (CISSS), a 6-item scale inquiring about symptoms of cold sensitivity involving the treated hand, with a score range from 4 (best) to 100 (worst) (87).
4. The palmar pain scale, a 2-item scale inquiring about pain in the palm and related activity limitations, with a score range from 0 (best) to 100 (worst) (3).
5. Pain VAS, with a score range from 0 (best) to 100 (worst).
6. Treatment satisfaction VAS, with a score range from 0 (best) to 100 (worst).
7. Medication use for pain in the treated hand (response options; no, sometimes, daily).

## **Treatment cost**

In *Paper VI*, direct treatment-related costs and indirect costs (sick-leave for employed patients) will be documented.

**Table 6. Study-specific outcome measurements**

<i>Paper</i>	Primary outcome	Secondary outcomes
<i>I</i>	Prevalence of doctor-diagnosed Dupuytren disease	Incidence Prevalence and incidence of treatment methods Number of healthcare visits and diagnosing facilities
<i>II</i>	Incidence of skin tears after collagenase treatment	Mean AED improvement Skin tears risk factors
<i>III</i>	Mean VAS difference at first injection (LA or modified collagenase)	Mean VAS difference between standard and modified collagenase injection method Mean VAS at second injection (modified collagenase in LA group) and during interval between injection and manipulation AEs
<i>IV</i>	Proportion of joints with recurrence (AED worsening $\geq 20^\circ$ ) between 5 weeks and 3 years	Mean AED from baseline to 5 weeks and 3 years (total and joint-specific) Proportion of joints with complete correction (PED 0-5°) Patient satisfaction Predictors of recurrence and dissatisfaction AEs
<i>V</i>	Adjusted mean AED and PED difference between examiners	Mean AED and PED
<i>VI</i>	Total AED improvement from baseline to 3 months Proportion of joints with recurrence (AED worsening $\geq 20^\circ$ ) between 3 months and 2 years	Total active motion (baseline to 3 months, 1, 2 and 5 years) Total AED (baseline to 1, 2 and 5 years) Total PED (baseline to 3 months, 1, 2 and 5 years) Proportion of joints with recurrence (AED worsening $\geq 20^\circ$ ) between 3 months and 5 years PROMs (QuickDASH, EQ-5D, CISS, palmar pain score, pain and satisfaction VAS) AEs Treatment cost

AED; active extension deficit, AE; adverse event, CISS; cold intolerance symptom severity scale, EQ-5D; EuroQol 5-dimensions, PED; passive extension deficit, PROM; patient-reported outcome measure, QuickDASH; disabilities of arm, shoulder and hand (11-item), VAS; visual analog scale.

**Table 7. Follow-up procedures during 5 years (Paper VI)**

	Baseline	Treatment (day 0)	1 week	3 weeks	6 weeks	3 months	1 year	2 years	5 years
Diagnosis, eligibility	X								
Randomization	X								
Surgery or injection		X							
Physical examination	X					X	X	X	X
AEs		X	X			X	X		
PROMs	X			X	X	X	X	X	X
Sick-leave		X				X	X		

AE; adverse event, PROM; patient-reported outcome measure.

### 3.4 Statistical analysis

The statistical tests used in the thesis are summarized below (Table 8). The data are presented as proportions and means with standard deviations (SD) or 95% confidence intervals (CI). In all *Papers (I-VI)*, a two-sided p-value of <0.05 is used to indicate statistical significance. The analyses were performed in SPSS (v 24) and STATA (v 14).

#### *Paper I*

For prevalence estimation we included individuals who received the diagnosis Dupuytren disease as the primary or secondary diagnosis. The denominator used was the population in Skåne Region on December 31, 2013. Private healthcare providers (account for approximately 27% of visits in the study region) do not report to the register. We reduced the denominator by 20% to account for this (lower reduction since most orthopedic and hand surgeons work in public healthcare in the region). For incidence estimation we identified individuals who consulted a medical doctor for Dupuytren disease in 2013 with no record of the diagnosis in the preceding 15 years, including only patients who received Dupuytren disease as the primary diagnosis. We calculated age and gender specific prevalence and incidence, and prevalence of treatment methods.

#### *Paper II*

We calculated the proportion of skin tears of any severity, classified by involved digit, location (distal palm, proximal digital crease or distal to that level) and size (<10 mm, 10-20 mm, >20 mm). Time-to-healing was classified into <1 week, 1-2 weeks and >2 weeks. Hands sustaining a skin tear were compared to hands that did not with regards to age, sex, previous surgical fasciectomy, injection-to-

manipulation interval, number of collagenase injections and severity of pretreatment contracture. Mean posttreatment AED was calculated (in the finger with the most severe AED in hands treated in more than 1 finger), at a median of 23 days (interquartile range 7-34). Data were missing in 5 patients. The Fisher exact test and t-test was used for categorical and continuous variables, respectively. Fixed-time Cox regression was used for adjusted analyses.

### *Paper III*

Sample size calculation was based on a clinically important VAS score difference of 13 (48, 128). A sample size of 50 patients per group was deemed appropriate to detect such a difference (90% power, 5% significance level, SD 2.0). We increased the sample size by 50% to cover a larger SD and to detect possible LA-related AEs. Mean VAS scores were calculated, using analysis of covariance adjusting for age, sex and injection-to-manipulation interval (for interval pain). Score for interval pain was not documented for 15 patients (administrative error).

### *Paper IV*

We calculated the proportion of treated joints with worsening  $\geq 20^\circ$  in AED from 5 weeks to 3 years. Mean AED was calculated at baseline, 5 weeks and 3 years, with the addition of mean PED at 3 years. The proportion of joints with complete correction (defined as PED 0-5 $^\circ$ ) was calculated. For patients who underwent limited fasciectomy after collagenase injection (n=2), the preoperative contracture values were used in the analyses. A paired t-test was used to statistically test AED changes from baseline to 5 weeks and 3 years. A mixed-effects logistic regression model was used to analyze predictors of recurrence (adjusting for sex and age), excluding thumb and index finger (n=3). Odds ratios (OR) were calculated for MCP and PIP joints separately. A Cox regression model was used to analyze predictors of patient dissatisfaction (adjusting for baseline factors), calculating relative risk (RR) for total AED.

### *Paper V*

Sample size calculation was based on a previous study investigating the inter-observer agreement in total PED in Dupuytren disease, finding a mean difference of 2.1 $^\circ$  (SD 10.3) in the left ring finger (22). A sample size of 189 joints was deemed appropriate to detect such a difference (80% power, 5% significance level, SD 10.3). We included joints (MCP or PIP) in the treated fingers with  $\geq 10^\circ$  of AED. We calculated mean AED and PED for the MCP and PIP joints measured by each of the three examiners. We used the t-test to compare the AED-PED differences according to joint (MCP vs PIP), finger (small vs ring), and sex (men vs women) and analyzed the correlation with age using the Pearson correlation coefficient (r). We performed a mixed effects model analysis (patients and fingers as random effects) and a fixed

effects model with robust variance (to account for patients providing multiple measurements) to determine the relationship between the size of the difference between AED and PED and the identity of the examiner, adjusting for affected joint, finger, sex, age, and AED.

### *Paper VI*

There is no universal definition of Dupuytren disease recurrence, although an expert group recently reached consensus that recurrence should be defined as more than 20° of contracture recurrence in any treated joint at 1 year (or later) (69). Sample size calculation is based on difference of 20° in total AED, which is deemed clinically relevant. Our hypothesis is that surgical fasciectomy is more effective in reducing recurrent contractures. In *Paper II*, patients treated with collagenase injection for recurrence after surgical fasciectomy had a mean improvement of 43° (SD 28) in total AED. To be able to show a difference of at least 20° in total AED between the groups at 3 months a sample size of 50 patients will be needed (80% power, 5% significance level, SD 25). We aim to recruit 56 patients to account for any potential loss to follow-up. If we encounter a higher drop-out rate during the course of the trial we will enroll more patients to achieve at least the pre-estimated sample size.

In the primary analysis we will calculate the mean between-group difference in improvement in total AED (MCP plus PIP) at 3 months. For the co-primary outcome we will calculate the proportion of joints (MCP and PIP separately) with worsening of at least 20° in total AED at 24 months compared to 3 months. When comparing patients rather than joints we will consider recurrence in any treated finger as an end-point. In the secondary analyses we compare the groups regarding change over time in QuickDASH score, EQ-5D index, palmar pain score, CISS score, pain VAS score and satisfaction VAS score. We will compare changes in total active motion, PED and total AED from baseline to 3 months, 12 months, 24 months and 60 months. We will calculate the proportion of joints with worsening of at least 20° in AED measured at 5 years compared to 3 months. All treated fingers are included in the primary analysis. For the primary outcome (changes in AED from baseline) a mixed model analysis will be used, which accounts for the fact that some patients provide data from multiple fingers, with and without adjusting for baseline factors. We will conduct 2 subgroup analyses; severity of baseline PIP contracture (<40° vs ≥40°) and number of previous collagenase injections (1 vs 2).

**Table 8. Summary of statistical tests used in the thesis**

	<i>Paper I</i>	<i>Paper II</i>	<i>Paper III</i>	<i>Paper IV</i>	<i>Paper V</i>	<i>Paper VI</i>
Prevalence/incidence	X					
t-test		X			X	
Paired t-test				X		
Pearson correlation coefficient					X	
Fischer exact test		X				
Analysis of covariance			X			
Cox regression		X		X		
Mixed-effects regression model				X	X	X
Fixed-effect regression model					X	

### 3.5 Ethics, dissemination, funding and potential conflicts of interests

For all studies (*Papers I-VI*) in the thesis study protocols have been reviewed and approved by the Regional Ethical Review Board, Lund University (*Paper I* 2014/276, *Paper II* 2013/656, *Paper III* 2015/134, *Paper IV* 2013/656, and *Paper VI* 2017/623). For *Paper V* the board waived the need for ethical approval. The studies have been and are conducted according to the Helsinki Declaration of 1975, as revised in 2000. Patients eligible for inclusion are given verbal and written information, and provide written consent at inclusion. *Paper VI* is registered in clinicaltrials.gov [NCT03406338], and complies with the CONSORT guidelines (116). All papers have been externally peer-reviewed and are published in international medical journals. The research was supported by Region Skåne and Kockska Foundation. The author of the thesis reports no conflicts of interests. The main supervisor was a member of an expert group on Dupuytren disease for Pfizer in 2012 and participated in meetings organized by Swedish Orphan Biovitrum (Sobi). The collagenase manufacturer did not support the research reported in this thesis or any of the authors. Patients in Figures 1, 5-8, 10-12 and 14 provided consent for publication in this thesis.

# Chapter 4: Results

## 4.1 Paper I

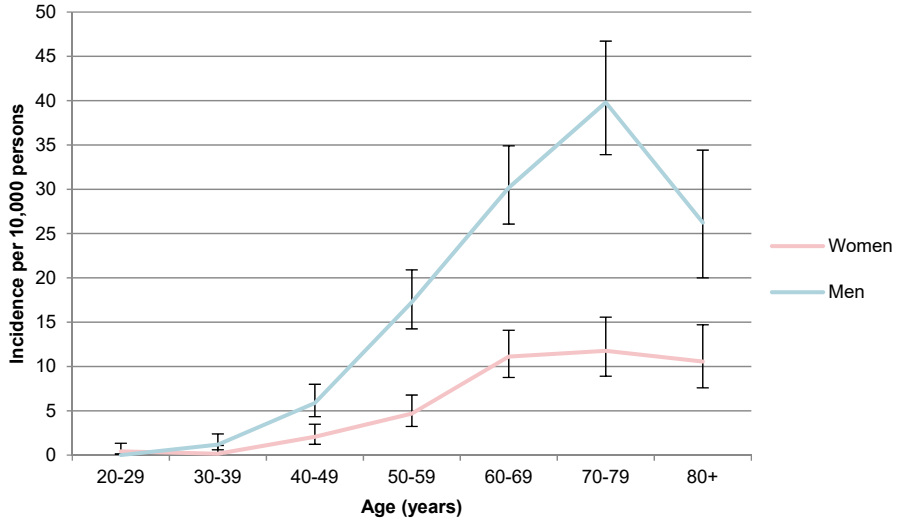
The overall prevalence of doctor-diagnosed Dupuytren disease was 0.92%. During the 16-year study period, 5208 of 7207 diagnosed individuals were men (72%). Prevalence increased with age in both genders; the highest age-specific prevalence was 4.6% in men and 1.5% in women, both at age  $\geq 70$  years (Table 9). The annual incidence in 2013 was 13.8 per 10,000 in men and 4.9 per 10,000 in women (Figure 13). The highest age-specific incidence was 40 per 10,000 in men aged 70-79 years. The majority of diagnosis (92%) were recorded at orthopaedic or hand surgery departments.

**Table 9. Prevalence of doctor-diagnosed Dupuytren disease during 1998-2013**

Age (years)	Men, n	Prevalence % (95% CI)	Women, n	Prevalence % (95% CI)
20-29	16	0.02 (0.01 to 0.04)	15	0.02 (0.01 to 0.04)
30-39	51	0.08 (0.06 to 0.10)	21	0.03 (0.02 to 0.05)
40-49	252	0.36 (0.32 to 0.41)	78	0.11 (0.09 to 0.14)
50-59	671	1.1 (1.0 to 1.2)	205	0.34 (0.30 to 0.39)
60-69	1554	2.6 (2.5 to 2.7)	575	0.94 (0.87 to 1.0)
70-79	1757	4.6 (4.4 to 4.8)	625	1.5 (1.4 to 1.6)
80-	907	4.6 (4.3 to 4.9)	480	1.5 (1.3 to 1.6)
Total	5208	1.35 (1.31 to 1.39)	1999	0.50 (0.48 to 0.52)

CI; confidence interval.





**Figure 13. Age and sex-specific incidence (with 95% confidence intervals) of doctor-diagnosed Dupuytren disease in 2013**

During the study period, 4025 diagnosed individuals (56%) were treated for Dupuytren disease, accounting for total 5853 interventions. In 2013, 526 individuals received a total of 580 treatments (Table 10). All treatments were almost exclusively given at orthopedic or hand surgery departments (99%).

**Table 10. Treatment trends in the study region during 1998-2013 and 2013 separately**

Treatment	1998-2013, n (%)	2013, n (%)
Fasciectomy	5064 (87)	274 (47)
Fasciotomy	319 (5)	45 (8)
Collagenase injection	224 (4)	224 (39)
Finger amputation	108 (2)	0 (0)
Unspecified injection	91 (2)	26 (5)
Other	47 (1)	11 (2)
Total	5853 (100)	580 (100)

## 4.2 Paper II

### *Skin tears*

Skin tears (Figure 14) occurred in 66 of 164 treated hands (40%). The small finger was involved in 39 hands (59%), the ring finger in 18 hands (27%), the middle finger in 8 hands (12%) and index finger in 1 hand. The location of the tear was in the distal palm in 20 hands (30%), at the level of the proximal digital crease in 27 hands (41%), and distal to the proximal digital crease in 19 hands (29%). The largest diameter of the tear was  $\leq 5$  mm in 30 hands (45%), 5-10 mm in 22 hands (33%) and  $>10$  mm in 14 hands (21%). Time-to-healing was  $<1$  week in 13 hands (20%), 1-2 weeks in 37 hands (56%) and  $>2$  weeks in 16 hands (24%). All wounds healed with open-wound treatment. No skin tear was infected or required surgical intervention. The severity of MCP joint contracture was identified as a risk factor for skin tear occurrence, with a mean difference in AED of  $27^\circ$  (95% CI 19-34) between hands sustaining a skin tear and hands with no tear. Hands that were given 2 injections were significantly more likely to sustain a skin tear, but they also had more severe MCP joint contractures. Age, sex, previous surgical fasciectomy and injection-to-manipulation interval were not significant factors for skin tear occurrence.



Figure 14. Skin tear in the small finger after the manipulation procedure

### *Treatment outcome*

Short-term outcome (median 23 days) was reported in 159 of 164 treated hands. Mean change in total AED (SD) was 55° (28). For all treated fingers, the mean total AED was 79° (34) before injection and 25° (25) at follow-up. Corresponding values for MCP joints were 43° (27) and 9° (14) and for PIP joints 36° (29) and 15° (18), respectively. Mean change in MCP joints was 39° (20) and in PIP joints 28° (19), including only joints with  $\geq 10^\circ$  pretreatment AED. In fingers with recurrence after previous treatment with surgical fasciectomy the mean change in total AED was 43° (28).

## 4.3 Paper III

Pain during collagenase injection was significantly worse without LA (Table 11). The mean VAS score (SD) for the modified injection without LA was 4.3 (2.5) and for LA injection 2.3 (1.7); adjusted mean difference 2.1 (95% CI 1.5 to 2.7). In the LA group VAS score during collagenase injection was 0.9 (1.0). The mean VAS score for the standard injection without LA was 4.8 (1.8), which did not differ from the modified injection without LA (adjusted mean difference 1.5 (95% CI -0.03 to 2.9)). No difference in mean VAS scores for pain during the injection-to-manipulation interval were observed between the groups. No AEs occurred related to the LA injection.

**Table 11. Pain visual analog scale scores for patients receiving a modified collagenase injection with or without local anesthesia**

	No LA		LA		Adjusted mean	
	n	Mean VAS (SD)	n	Mean VAS (SD)	difference (95% CI)	P value
First injection <sup>a</sup>	78	4.3 (2.5)	83	2.3 (1.7)	2.1 (1.5 to 2.7)	<0.001
Interval <sup>b</sup>	67	2.9 (1.9)	79	2.9 (2.3)	0.1 (-0.6 to 0.8)	0.79

<sup>a</sup>Collagenase in No LA group and buffered mepivacaine in LA group; mean differences adjusted for sex and age.

<sup>b</sup>Interval between injection and manipulation (1 or 2 days); mean differences adjusted for sex, age and interval. CI; confidence interval, LA; local anesthesia, SD; standard deviation, VAS; visual analog scale.

## 4.4 Paper IV

### *Treatment outcome*

3-year outcomes were available for 83 (97%) patients (89 hands, 120 fingers). Between the 5-week and 3-year measurements, AED worsened by  $\geq 20^\circ$  in 17 MCP (14%), 28 PIP (23%), and in either joint in 41 (34%) fingers. The mean total AED (SD) was 75° (39) before injection, 21° (26) at 5 weeks and 32° (29) at 3 years, for

all treated fingers (Table 12). The corresponding values for MCP joints were 44° (25), 9° (15), and 12° (17), and for PIP joints 31° (29), 12° (17) and 20° (24), respectively. Complete correction (PED 0°-5°), in treated joints with baseline AED ≥10°, at the 3-year follow-up was observed in 79 of 108 (73%) MCP and 25 of 72 (35%) of PIP joints.

**Table 12. Active extension deficit before (baseline), 5 weeks and 3 years after injection**

	Baseline	5 weeks	3 years	Mean difference (95% CI)	
	n=126	n=126	n=120	Baseline to 5 weeks	5 weeks to 3 years
MCP	44 (25)	9 (15)	12 (17)	35 (31 to 39) <sup>a</sup>	-4 (-6 to -1) <sup>b</sup>
PIP	31 (29)	12 (17)	20 (24)	19 (15 to 22) <sup>a</sup>	-9 (-12 to -6) <sup>a</sup>
Total	75 (39)	21 (26)	32 (29)	54 (49 to 58) <sup>a</sup>	-13 (-16 to -9) <sup>a</sup>

Values are mean (SD) degrees unless specified otherwise. Number of fingers (n) in 86 patients (83 patients at 3 years). CI; confidence interval, MCP; metacarpophalangeal, PIP; proximal interphalangeal. <sup>a</sup>p<0.001, <sup>b</sup>p=0.002.

### *Predictors of recurrence*

Treatment of small finger PIP joint contracture, greater severity of pretreatment contracture and previous fasciectomy on the treated finger were significant predictors of contracture recurrence (Table 13). The OR (95% CI) for ring finger PIP joint contracture (vs small finger) was 0.20 (0.05 to 0.72), for increasing baseline severity (per degree) of MCP contracture 1.06 (1.03 to 1.09) and of PIP contracture 1.08 (1.05 to 1.12), and for previous fasciectomy (MCP joint) 7.23 (1.35 to 38.8). Age and sex had no significant association with recurrence.

**Table 13. Predictors of recurrence at 3 years**

Variable (referent category/unit)	MCP OR (95% CI)	PIP OR (95% CI)
Sex (male)	2.2 (0.5 to 9)	4.1 (1.1 to 15)
Age (per year)	1.03 (0.95 to 1.11)	1.08 (1.01 to 1.16)
Finger (small)	Ring	0.2 (0.05 to 0.7) <sup>a</sup>
	Middle	0.3 (0.05 to 1.12)
Baseline contracture (per degree)	1.06 (1.03 to 1.09) <sup>b</sup>	1.08 (1.05 to 1.12) <sup>b</sup>
Recurrence after fasciectomy (no)	7.2 (1.4 to 39) <sup>c</sup>	3.2 (0.7 to 16)
Injection-manipulation interval (1 day)	0.9 (0.3 to 3)	1.0 (0.3 to 2.9)

Mixed effects regression model (data from 117 treated fingers, excluding thumb and index finger). CI; confidence interval, MCP; metacarpophalangeal, OR; odds ratio, PIP; proximal interphalangeal. <sup>a</sup>p=0.01, <sup>b</sup>p<0.001, <sup>c</sup>p=0.02.

### *Patient satisfaction*

Patients reported satisfaction with outcome in 87 of the 92 treated hand; very satisfied in 39 hands (46%), satisfied in 20 patients (24%), neutral in 12 hands (14%), and dissatisfied in 16 hands (19%). Mean improvement in total AED (SD)

from baseline to 3 years was 47° (34) among very satisfied and satisfied patients and 22° (22) among dissatisfied patients; mean difference 25° (95% CI 13 to 37). Patient dissatisfaction was higher with increasing pretreatment contracture severity (RR 1.02, 95% CI 1.01 to 1.04) and with contracture recurrence (RR 1.03, 95% CI 1.02 to 1.05). Age and sex had no significant association with dissatisfaction.

#### *Reinjections, subsequent surgery and adverse events*

4 patients received a second collagenase injection during the study period at 4, 8, 12, and 24 months after the first injection, respectively. 2 other patients underwent limited fasciectomy at 6 months and 3 years after injection, respectively. No other patients had any other surgical interventions during the study period. At the 5-week and 3-year follow up visit the hand therapist did not observe and the patients did not report any AEs. No patient suffered from neurovascular injury, flexor tendon rupture, infection or complex regional pain syndrome during the study period.

## 4.5 Paper V

A total of 157 consecutive patients (81% men), mean age 70 (SD 8) years, were examined. AED of  $\geq 10^\circ$  was recorded in 291 joints (163 MCP and 128 PIP) and these were included in the analyses. The affected finger was the small (57%), ring (36%), middle (6%) and index (1%). For all 291 joints mean AED (SD) was 46° (21) and mean PED (SD) was 37° (23). Examiner 1 measured 115 joints, examiner 2 measured 83 joints, and examiner 3 measured 93 joints (Table 14). Mean difference (SD) between AED and PED measured by examiner 1 was 6° (6), by examiner 2 was 9° (9), and by examiner 3 was 12° (9). No statistically significant AED-PED differences were found according to joint (MCP mean 9 [8], PIP 8 [8]), finger (small 9 [9], ring 9 [7]), sex (men 10 [10], women 9 [7]), or age ( $r=-0.04$ ).

**Table 14. Patient characteristics according to examiner**

		Examiner 1	Examiner 2	Examiner 3
Patients, n		60	49	48
Joints, n		115	83	93
	Men, n (%)	87 (76)	72 (87)	77 (83)
	Women, n (%)	28 (24)	11 (13)	16 (17)
Age, mean (SD) years		69 (7)	70 (9)	70 (9)
Affected finger, n	Small	70	41	54
	Ring	34	37	35
	Middle	11	5	2
	Index	0	0	2
	Thumb	0	0	0
MCP joints, n		65	50	48
PIP joints, n		50	33	45
MCP joint, mean (SD) degrees	AED	53 (24)	47 (16)	46 (22)
	PED	47 (16)	36 (21)	33 (25)
PIP joint, mean (SD) degrees	AED	42 (21)	35 (19)	45 (19)
	PED	37 (21)	27 (22)	34 (20)

AED; active extension deficit, MCP; metacarpophalangeal, PED; passive extension deficit, PIP; proximal interphalangeal, SD; standard deviation.

The mixed effects model analysis showed that the identity of the examiner was a significant determinant of the AED-PED difference, with adjusted mean difference of 4.0, 6.5, and 2.5 for examiner 2 vs 1, examiner 3 vs 1, and examiner 3 vs 2, respectively (Table 15).

**Table 15. Difference between active and passive extension deficit measured by 3 examiners**

Examiner	Adjusted mean difference	95% confidence interval
2 vs 1	4.0	1.7-6.3
3 vs 1	6.5	4.2-8.8
3 vs 2	2.5	0.1-4.9

Values are mean difference in degrees, adjusted for affected joint, finger, age, sex and active extension deficit (mixed effects model).

## 4.6 Paper VI

Paper VI is a study protocol of an ongoing randomized controlled trial. Since no interim analysis will be performed, no results are available in this thesis. To date, 21 of 56 patients have been recruited to the study (November 14, 2019).



# Chapter 5: Discussion

## 5.1 Dupuytren disease - an endemic population disease with significant healthcare burden

Dupuytren disease is a common medical condition in the general population, especially in western countries (74). Although the majority of affected individuals only have minor soft tissue changes in the palm causing no functional limitations, we have shown in *Paper I* that the prevalence of clinically important Dupuytren disease is high. The prevalence and incidence of doctor-diagnosed Dupuytren disease was clearly correlated with age, rapidly increasing after 50 years with a peak in individuals 70 years and older. Our prevalence estimates are, however, slightly lower in comparison to other studies examining the prevalence of contractures in random population samples of individuals older than 50 years (4-8%) in northern European countries (29, 54, 77). A possible explanation is that some individuals with mild contractures have no functional limitations, and therefore do not seek medical advice.

Almost 75% of diagnosed individuals were men (*Paper I*). The male predominance is reported in most studies on Dupuytren disease epidemiology (61). However, in a previous study assessing prevalence of Dupuytren disease in the Netherlands, the male-to-female ratio (1.2:1) was significantly lower (77). An explanation to this discrepancy is that men have an earlier disease onset and are more likely to develop contractures that require medical consultation and treatment (140).

In *Paper I*, more than half of the diagnosed individuals underwent treatment for Dupuytren disease. Importantly, many patients were treated more than once, likely due to bilateral disease, disease extension or recurrence, and a large number of healthcare visits were observed (mean 6 visits per patient). This finding shows a significant clinical burden of Dupuytren disease on the healthcare system, which will likely increase in the future with an aging population with high functional demands. The finding may therefore be useful in healthcare planning and resource allocation, and it also highlights the need for continuous research on Dupuytren disease to improve treatment.



## 5.2 The impact of collagenase on treatment for Dupuytren disease

Traditionally, surgical fasciectomy has been the most common treatment method used for Dupuytren disease. In *Paper I*, surgical fasciectomy was the method of choice in the study region during 1998-2013. This finding is concordant with other international studies during the same time period. According to a survey of hand surgeons in 12 European countries about their treatment of Dupuytren disease, surgical fasciectomy was used in 70-80% of patients in 2008 (31). Data from the Hospital Episodes Statistics database in England showed that between 2003 and 2007, fasciectomy constituted 91% of surgical treatments for Dupuytren disease (51). A similar trend was observed in Canada, with surgical fasciectomy accounting for about 95% of the surgical procedures between 2005 and 2010 (83).

How did the introduction of collagenase injection impact treatment trends? In *Paper I*, collagenase treatment constituted almost 40% of treatments in Skåne region 2013. This major trend shift was at the expense of surgical fasciectomy, whereas the number of fasciotomies remained stable (around 8% of treatments). A similar trend was observed in a study assessing the impact of collagenase in the United States between 2007 and 2013, and also noted an increased number of treated patients after the introduction (142). According to data from The National Quality Register for Hand Surgery in Sweden, hand surgery departments using collagenase injection have decreased the use of surgical fasciectomies with 82% (56). At the study center of the thesis (Hässleholm-Kristianstad Hospitals) the number of surgical fasciectomies have decreased from 125 procedures in 2010 to 15 procedures in 2017, with a slight increase in 2018 to 31 procedures partly explained by the ongoing randomized controlled trial (*Paper VI*). Other treatment facilities in the study region that have not adopted collagenase treatment routinely do not show the same decrease in the number of surgical fasciectomies (Appendix). The reported treatment trends suggest that collagenase injection can replace surgical fasciectomy to a large extent. Needle fasciotomy may be more limited in this respect, although the number of performed procedures may be underreported. When assessing treatment-related costs of a minimally-invasive procedure for Dupuytren disease, the number of performed surgical fasciectomies has to be taken into consideration in an overall cost-effectiveness analysis, since surgery is associated with higher cost than collagenase injection (4, 117).

### 5.3 Collagenase injection – treatment protocol evolution and current state of use

Since the initial multicenter trial the treatment protocol of collagenase injection has evolved, with a resulting modified treatment method used in the studies of this thesis.

LA was not used in the original trial (65), since it could be considered a confounding factor. LA before the manipulation procedure soon became standard practice, and has been shown to be safe (86). The manipulation procedure is painful, and the introduction of LA may therefore enable a more optimal contracture reduction resulting in a better treatment outcome. Furthermore, in *Paper III* we found that the use of LA before collagenase significantly reduced the injection-related pain, and has now become standard practice at our department. Decreased collagenase injection-related pain may optimize drug deposition in the cord, although whether this has any effect on the clinical outcome needs to be further investigated.

The use of a higher collagenase dose has become more widespread, and has been shown to be safe and effective (26, 49, 53). Using a higher dose, sometimes 2 vials, enables the surgeon to treat multiple joints in 2 or more fingers in one session instead of treating joints separately with a 30-day interval. This regime facilitates a more effective management of patients treated for Dupuytren disease with collagenase injection and decreases treatment-related costs.

In *Papers II and IV*, no severe AEs have been observed using the modified treatment method. We have, however, observed a large proportion of skin tears (40% of treated hands) at the manipulation procedure. The incidence of skin tears in *Paper II* is higher than reported in other studies (1, 65, 119, 135). This finding may have several explanations. First, incidence of skin tears was the primary outcome of the study and tears of any size were documented. Second, the modified method using a higher dose treating multiple joints may have contributed to the higher tear incidence. Finally, our aim at the manipulation procedure is always to achieve optimal contracture reduction despite skin tear occurrence, which is enhanced by the use of LA. As shown in *Paper II*, the healing potential of skin tears is excellent, with no infections or additional surgical procedures required. Skin tears should therefore not be viewed as an AE, but rather a sign indicating successful contracture treatment, and it is important to give this information to the patient before treatment.

Patient satisfaction with collagenase is high, but deteriorates in patients suffering from recurrence (20). Although two-thirds of patients in *Paper IV* reported being very satisfied or satisfied with treatment at 3 years, 18% were dissatisfied. Dissatisfaction correlated with recurrence. Predictors of recurrence were identified

as severe pretreatment contracture, small finger PIP joint contracture and previous surgical fasciectomy. Identifying and informing these patients may help in meeting their treatment expectations.

## 5.4 Which treatment method should be used for Dupuytren disease?

A Cochrane review on Dupuytren disease treatment has concluded that there is insufficient evidence to show the relative superiority of different surgical procedures (107). Comparison between studies are limited from several aspects:

1. *Patient selection.* Dupuytren disease covers a large spectrum of disease severity. Patients with nodules (27) or isolated mild to moderate MCP joint contractures (89, 126) have a good treatment prognosis irrespective of treatment method, whereas PIP joint contractures, combined moderate to severe contractures and patients with recurrence do much worse (57, 98, 133).
2. *Definitions.* Recurrence and definition of clinically relevant contracture reduction vary between studies (137), affecting sample size calculation and reporting of results.
3. *Outcome measurement.* Both primary and secondary outcome measures vary between studies, and are not always reported in a standardized manner (103). An example is the use of AED or PED, which varies significantly between examiners, as shown in *Paper V*. PED is most commonly used in studies, although AED may be a better measure of functional outcome and is less examiner-dependent. Reporting both measurements in a standardized protocol should be encouraged. Furthermore, it is important to have an independent outcome assessor, to avoid surgeon's bias. Finally, there is a great need for a validated universal disease-specific PROM.
4. *Follow-up length.* Recurrence is often a slowly progressing process, and few studies report outcomes at 3 years or longer. An example highlighting the importance of adequate follow-up length is the randomized controlled trial by Selles et al. comparing limited fasciectomy versus needle fasciotomy with lipofilling. The study found no significant difference in outcome at 1 year, but a significantly higher recurrence rate in the needle fasciotomy group at 5 years (118).

In recent years Dupuytren disease researchers have collaborated to create uniform definitions (69), and also recommendations regarding outcome measurements

standardization (12, 103). Considering current treatment variations and lack of agreement among surgeons (92), it is important to enable comparison between studies to provide evidence for best practice.

Is there any difference between collagenase injections using the standard or the modified injection method? In the Collagenase Option for Reduction of Dupuytren Long-Term Evaluation of Safety Study (CORDLESS) 643 of 950 of the initial study participants could be evaluated 3 years after treatment with the standard technique (99). At 3 years, “worsening” of contracture (defined as  $\geq 20^\circ$  increase in contracture in fully or partially corrected joints with or without a palpable cord, or subsequent treatment) was observed in 28% of MCP joints and 58% of PIP joints. A study of 47 patients with isolated MCP joint contracture treated with a single 0.58 mg collagenase injection, reported a recurrence rate (defined as contracture  $> 20^\circ$ ) of 25% at 2 years (89). A study of 66 patients with both MCP and PIP joint contractures evaluated 2 years after collagenase injection showed  $\geq 20^\circ$  increase in extension deficit in 28% of MCP joints and 62% of PIP joints (131). In *Paper IV*, recurrence (AED worsening  $\geq 20^\circ$ ) occurred in 14% of MCP joints and 23% of PIP joints. The improved results may be explained by the modified injection method, using LA before both injection and manipulation, and the aim to achieve optimal contracture reduction despite skin tear occurrence. It has to be remembered that collagenase injection is still a relatively new treatment method, and modifications of treatment protocols and experience may improve results in the future.

In a randomized controlled trial comparing needle fasciotomy versus limited fasciectomy, with recurrence defined as  $\geq 30^\circ$  in total PED from 6 weeks to 3 years, the authors reported a recurrence rate of 9% of hands in the limited fasciectomy group and 63% hands in the needle group (133). Using the same definition, recurrence in *Paper IV* occurred in 21% of hands.

Randomized controlled trials comparing needle fasciotomy versus collagenase injection for predominantly MCP joint contractures have been reported with up to 3 years follow-up, with no significant difference in treatment outcome (115, 126). It has to be remembered that these studies only evaluate a selected part of the Dupuytren spectrum and may not represent the majority of Dupuytren patients undergoing treatment. In the study by Strömberg et al. 728 (82%) of 844 patients assessed for eligibility were excluded for non-specified reasons (126). In comparison, the study population in *Paper IV* represent a larger spectrum of Dupuytren patients, including severe combined contractures and even patients treated for recurrence (11 patients, 15 treated fingers). The authors of these trials suggest an advantage for needle fasciotomy, foremost based on the initial treatment cost. However, as discussed above, an overall cost-effective analysis of Dupuytren disease has to take the number of performed surgical fasciectomies into consideration, since surgery is associated with higher cost than collagenase (4, 117). During the study period of *Paper IV*, surgical fasciectomies constituted only 27%

of treatments for Dupuytren disease, with a further decrease in the following years (Appendix).

In a randomized controlled trial comparing needle fasciotomy versus collagenase injection for isolated PIP joint contractures, no significant difference in treatment efficacy was found at 2 years (120). In that study 28 of 29 (97%) of patients treated with collagenase had a PIP joint contracture in the small finger, compared to 15 of 21 (71%) in the needle fasciotomy group. In *Paper IV*, we have identified small finger PIP joint contractures as a predictor of recurrence. This finding suggest that future randomized controlled trials should be stratified according to small finger involvement, which we have applied for our ongoing randomized controlled trial (*Paper VI*).

Is it possible to draw any conclusions on which treatment method that should be used for Dupuytren disease? Clearly, further randomized controlled trials and large prospective cohort studies are needed to answer this question. It also depends on the patients' treatment preferences and expectations. Based on current evidence, surgical fasciectomy is associated with the lowest recurrence rate (33, 130, 133), but the procedure is associated with higher risk of severe AEs, prolonged hand recovery (30, 32, 44), and higher cost than the minimally-invasive treatment options. Patients with isolated mild to moderate MCP joint contractures have a favorable prognosis, and needle fasciotomy seems to be as effective as collagenase injections for this patient group, at least in the medium-term, with the advantage of lower initial direct treatment-related cost (115, 126). In the treatment of combined MCP and PIP joint contractures, needle fasciotomy has a high recurrence rate. In this patient group, representing the majority of patients with function-limiting contractures requiring treatment, collagenase using a modified injection method can be used safely and with a reasonable recurrence rate. As shown in *Paper IV*, collagenase injection is a versatile treatment method that also can be used for severe contractures and recurrence in patients requesting a minimally-invasive procedure, and it can replace the need for open surgery to a large extent.

## 5.5 Recurrence - a difficult clinical problem

Despite the growing interest and advances in the treatment of Dupuytren disease, the fact remains that no cure exists. Recurrence after Dupuytren disease is common irrespective of treatment method. Recurrence is a difficult clinical problem. First, patients treated for recurrence have an increased risk of re-recurrence, as shown in *Paper IV*. Second, the anatomy may be distorted by scar tissue after previous intervention and the disease may recur without a palpable cord, limiting the use of traditional treatment. Recurrence is usually treated by surgical fasciectomy, although technically more challenging and with a higher complication rate than the

index surgery (30). In cases of severe recurrence without a palpable cord, salvage procedures have to be considered, for example PIP joint fusion and amputation (28, 71), or the new recently reported finger-preserving procedure involving middle phalanx resection and ligament reconstruction to create a functioning interphalangeal joint (39).

Research on minimally-invasive treatment for Dupuytren disease has primarily focused on first-time treatment, but its use in recurrence has also been studied, showing good short-term results (15, 134). To our knowledge, no previous or ongoing randomized controlled trial has compared surgical fasciectomy versus collagenase injection for recurrent Dupuytren disease. The aim of the study described in the final paper of this thesis is to provide evidence regarding the most effective treatment method for recurrence, and also evaluate safety, PROMs and cost of treatment.



# Chapter 6: Strengths and limitations

## 6.1 General

This thesis has studied Dupuytren disease from a wide perspective covering epidemiology, outcome measures and treatment outcome. All clinical studies are prospective, and add information regarding Dupuytren disease treatment where the previous literature is scarce or absent. Although the thesis does not compare collagenase injection directly with other treatment methods used for primary Dupuytren disease, it includes a study protocol for an ongoing randomized controlled trial comparing treatment methods for recurrent disease.

## 6.2 Study-specific

### *Paper I*

A strength of *Paper I* is the population-based design. The healthcare register is reported to by all hospitals in Skåne region. It is unlikely that patients with Dupuytren disease have sought care outside the region, since there are no hand surgery units in the bordering regions. Another important strength is the research question, focusing on patients seeking medical consultation for Dupuytren disease, giving an estimate of clinically relevant disease and its burden on the healthcare system.

The main limitation of *Paper I* is that private healthcare providers do not report to the register, but this was accounted for by a 20% deduction of the population denominator. Furthermore, the register does not contain data on contracture severity, and repeated treatment cannot be differentiated from bilateral treatment. Diagnosis is made by different doctors (primary, secondary and tertiary levels), although the majority was made at orthopedic and hand surgery departments. Finally, the estimates may be generalizable to northern Europe (29, 54, 77) and North America (34), but not to other populations worldwide where the prevalence is much lower (50, 141). In terms of prevalence of treatment methods, procedures such as collagenase injection and needle fasciotomy may be underreported, since they are performed in an outpatient setting.



### *Papers II-V*

The main strength of *Papers II-V* is the prospective study designs. All studies evaluate consecutively treated patients with a high participation rate. The study center is an orthopedic department to which the vast majority of patients with Dupuytren disease are referred; this should enhance the generalizability of the study results. In all studies the outcome measurements are performed using standardized protocols and independently of the treating surgeon.

Limitations of the treatment outcome studies (*Papers II and IV*) include a moderate sample size and a single center. No follow-up evaluations were performed between 5 weeks and 3 years; such evaluations could have provided more information regarding recurrence pattern and patient experience. At baseline and 5 weeks after treatment only AED was measured, with PED added at 3 years to enable comparison with other studies. Another limitation is the absence of PROMs, limited to a satisfaction score in *Paper IV*. More information on patient view on collagenase treatment could have been obtained by the addition of more PROMs. However domain-specific measures, such as DASH, have shown only modest responsiveness in Dupuytren disease (106, 108) and disease-specific measures, such as Unité Rhumatologique des Affections de la Main scale (16), may need further independent validation (110).

In *Papers III and V*, the non-randomized allocation is a limitation, and randomization would have reduced the risk of bias and increased the strength of the studies.

In *Paper III*, the patients were scheduled by an administrative assistant by alternation independently of the treating surgeon. Furthermore, the baseline characteristics of the patients were similar and no differences were seen between groups in VAS scores for pain during the injection-to-manipulation interval. Another limitation is that the number of patients in the group that received collagenase injection with the standard method without LA was smaller than the pre-estimated sample size. However, the 95% CI for the mean difference from the group that received collagenase using the modified injection method did not include a clinically important difference in favor of the standard method. This indicates that the sample was adequate to show that the pain associated with collagenase injection was not related to the injection method. Finally, the use of the subjective VAS score as the primary outcome measure is a possible limitation, however, it is one of the most commonly used pain measures in research and clinical practice.

In *Paper V*, inter-observer reliability of AED and PED differences was assessed using a non-conventional method. The examiners measured joints of different patients with a non-randomized allocation. The allocation of patients was, however, done without knowledge of the identity of the present hand therapist at the given treatment session and baseline patient characteristics were similar. A conventional design would have been to have all examiners measure the same patients in a

random order, in which case differences in AED and PED between examiners could be analyzed. Broekstra et al. examined the inter-observer reliability between 2 examiners measuring total PED in patients with Dupuytren disease and found a moderate (middle finger) to high inter-observer agreement (intraclass correlation coefficient 45-98.5%) (22). Before study start, the 2 examiners evaluated 50 patients together. We used a different approach to assess agreement between examiners, enabling the use of a substantially larger sample than would have been practically possible if all patients would have been examined by the 3 therapists. Besides, the therapists were unaware of the concept being studied. A possible strength of this concept is that it would apply to hand therapists in general, especially when measurements across studies are being compared. To compensate for differences between patients measured by the 3 examiners and potential variations in AED measurements (43), we applied a mixed effect model with robust variance for adjusted analysis. Our results show that the difference between AED and PED was similar in relation to all baseline variables (joint, finger, age, sex and AED) except for the identity of the examiner.

#### *Paper VI*

The main strength of *Paper VI* is the randomized controlled design. The study center is an orthopedic department to which the vast majority of patients with Dupuytren disease in the study region are referred. A single blinded outcome assessor (experienced hand therapist not involved in the treatment of the trial participants) will perform standardized follow-up measurements, independently of the treating surgeons. The study setting, a single center, may also be considered a limitation. A multi-center trial, involving several surgeons (who may use different surgical techniques), would be more pragmatic and increase generalizability. We have chosen to involve only one experienced hand surgeon to perform the open surgical procedures in this trial in order to provide optimal conditions for achieving the best possible results that will be compared with the results of collagenase injections. A detailed description of surgical techniques used in the trial (for example, proportion of participants treated with limited fasciectomy only, fasciectomy combined with additional procedures addressing secondary PIP joint contractures, skin graft, or other procedures) will be presented.

The number of patients planned to be enrolled in this superiority trial is based on the pre-trial estimation of the sample size needed to compare the treatment methods with regard to the primary outcome. However, a larger sample would yield greater precision of the estimates in the primary and secondary analyses and the sub-group analyses. Another possible limitation of the study is the length of follow-up for the primary outcome. Recurrence of contracture in Dupuytren disease is often a slow process that might not occur by 24 months after treatment. Furthermore, the literature lacks a clear universal definition of disease recurrence and what

constitutes a clinically relevant difference in total extension deficit, although an expert group recently reached a consensus that recurrence should be defined as more than 20° of contracture recurrence in any treated joint at 1 year post-treatment (or later) compared to 6 weeks post-treatment (69). This in turn may affect the sample size calculation. We based our calculation on a clinically relevant difference of 20° since it has been used by recent studies on collagenase treatment (98, 99), and is supported by the expert group (69). Another limitation is the use of PROMs in research on Dupuytren disease, since available tools either show modest responsiveness to contracture changes or are in need of further independent validation, as discussed above. Furthermore, the study is performed in Sweden and cost-analysis may not be generalizable to other countries.

# Chapter 7: Conclusions

## *Paper I*

Dupuytren disease is a common cause of medical consultation, with a strong correlation with higher age and male sex. More than half of diagnosed individuals underwent treatment during the 16-year study period. Many patients underwent treatment more than once, with a mean of 6 visits to healthcare personnel, indicating a substantial healthcare burden. Surgical fasciectomy was the most commonly used treatment method during the study period, with a shift to increased use of collagenase injection in 2013 in the study region.

## *Paper II*

Skin tears occurred in 40% of treated hands, most commonly in the small finger (59% of tears). The diameter was  $\leq 10$  mm in 79% of skin tears. All skin tears healed with open-wound treatment (75% within 2 weeks). No skin tear required additional surgical intervention or became infected. Severity of MCP joint contracture was identified as a risk factor for skin tear occurrence. Short-term (median 23 days) treatment outcome was good (mean total AED improvement 55°).

## *Paper III*

Administration of LA, as a proximal digital nerve block, can significantly reduce the overall collagenase injection-related pain (mean VAS difference 2.1). The modified injection method was not more painful than the standard injection method. No differences were found between groups in pain scores during the injection-to-manipulation interval. No AEs occurred related to LA administration.

## *Paper IV*

In a prospective cohort study with a near-complete follow up assessing collagenase treatment outcome at 3 years, no recurrence was observed in two-thirds of treated fingers. Complete correction (PED 0-5°) was observed in 3 of 4 MCP joints but only in a third of PIP joints. No AEs were reported and two-thirds of the patients were satisfied. Identified predictors of recurrence were small-finger PIP joint contracture, more severe baseline contracture and treatment for recurrence.

### *Paper V*

Measurement of PED varies significantly between examiners, adjusting for finger, joint, age, sex and AED. This finding highlights the need for outcome measurement standardization in Dupuytren disease research, including both AED and PED, to enable comparisons across studies.

### *Paper VI*

The final study of the thesis is an ongoing randomized controlled trial comparing surgical fasciectomy and collagenase injection for recurrent Dupuytren disease, evaluating treatment efficacy, safety, PROMs and cost.

# Chapter 8: Future perspectives

The introduction of collagenase injection has offered a new method of treating Dupuytren disease, but we still do not have an optimal treatment method and the search for a cure continues.

The cure for Dupuytren disease will not be found in the currently used treatment methods, but both surgical fasciectomy and the minimally-invasive treatment methods have a potential to improve, which warrants continuous future research. Randomized controlled trials and large high-quality prospective cohort studies with long-term follow up will be needed to improve treatment outcome and provide evidence on optimal use of the treatment methods. A Dupuytren disease register would also be helpful to examine larger samples of Dupuytren patients enabling stronger sub-group analysis. This will make it possible to identify patient groups within the spectrum of Dupuytren disease that are best suited for a certain procedure. Another area of improvement is to make Dupuytren disease research homogenous to enable comparison between studies, including standardization of definitions and outcome measurements. Development of validated disease-specific PROMs would also improve Dupuytren research.

The use of collagenase as a therapeutic agent is not limited to Dupuytren disease. Research has explored collagenase use for other indications, including Peyronie disease (47), frozen shoulder (9), and cellulites (111), with promising results. More potential areas of collagenase use may be found in the future.

In recent years, multiple studies have explored the pathogenesis of Dupuytren disease on a genetic and molecular level. These insights give new ideas and hope for a future cure. A future treatment may target specific genes or cytokines, to inhibit disease progression at an early stage (95). Furthermore, the knowledge gained from preclinical Dupuytren research may be used to improve knowledge on other diseases characterized by fibrosis development.

To conclude the thesis, what was the best thing with the introduction of collagenase treatment for Dupuytren disease? The obvious answer is the addition of an effective, safe minimally-invasive treatment option. In a larger perspective, an even more important impact is the increased interest in Dupuytren disease that followed the introduction, both among treating surgeons and patients, intensifying research on the disease and the search for a final cure.



# Summary in Swedish

## Populärvetenskaplig sammanfattning

Trots att namnet är okänt för allmänheten så bör Dupuytren's sjukdom klassas som en folksjukdom. Denna handsjukdom, som kännetecknas av ökad produktion av proteinet kollagen i handflatans bindvävnad, är framförallt vanlig i västvärlden där 20-30% av män i pensionsåldern beräknas vara drabbade. Lyckligtvis drabbas majoriteten enbart av förhårdnader i handflatan, vilket inte påverkar handens funktion. Hos en ansevärd mängd patienter är sjukdomen dock mer aggressiv, med utveckling av hårda strängar i handflatan som ger upphov till böjda fingerleder som inte går att sträcka (kontrakturer). En enkel sak som att ta upp plånboken ur byxfickan eller bära handskar på vintern kan vara omöjligt för en patient som utvecklat Dupuytren's kontraktur.

Den franske kirurgen Guillaume Dupuytren beskrev sjukdomen år 1831 och demonstrerade samtidigt en teknik för kirurgisk behandling. Trots att det gått nästan 200 år är kunskapen om Dupuytren's sjukdom fortfarande begränsad. Den specifika orsaken till sjukdomen är inte klarlagd, men det är känt att sjukdomen är ärftlig och att vissa yttre faktorer kan kopplas till ökad risk för att drabbas (exempelvis manuellt handarbete, tidigare handskada, diabetes, rökning). Det finns fortfarande inget bot för Dupuytren's sjukdom. Den vanligaste behandlingen idag är fortfarande kirurgi som går ut på att avlägsna den sjuka bindvävnaden i handflatan (fasciektomi). Kirurgisk fasciektomi är en effektiv metod för att räta ut kontrakturdrabbade fingrar. Risken för allvarlig komplikation, exempelvis nerv-kärlekskada och infektion, är dock relativt hög. Lång rehabiliteringstid och sjukskrivningsperiod i upp till tre månader krävs ofta efter ingreppet. Kirurgiskt ingrepp innebär också en hög behandlingskostnad. Trots operation drabbas många patienter av kontrakturåterfall, och en ny operation är då mer tekniskt krävande och har en ännu högre komplikationsrisk. I slutändan kan amputation vara det enda kvarstående behandlingsalternativet.

Positivt är att intresset kring Dupuytren's sjukdom ökat under de senaste åren, mycket tack vare ett ökat intresse för nya minimal-invasiva behandlingsalternativ som nålfasciotomi och kollagenasinjektion. Kollagenasinjektion godkändes år 2010 som den första läkemedelsbehandlingen för Dupuytren's kontraktur. Behandlingen består av injektion av enzymet kollagenas som bryter ner kollagenet i



bindvävssträngen, och därefter sträcks fingrarna raka följande dag. Fördelar i jämförelse med kirurgi är behandlingens enkelhet, gynnsamma biverkningsprofil (inga nerv-kärlskador), snabb återhämtning av handfunktionen (1-2 veckor) samt lägre behandlingskostnad då behandlingen utförs på mottagning och inte kräver operationssalens resurser. Trots de tilltalande fördelarna är den vetenskapliga litteraturen kring behandling med kollagenasinjektion begränsad. Syftet med denna avhandling var att studera och tillföra kunskap om Dupuytrens sjukdom, med fokus på behandling med kollagenasinjektion.

I *studie 1* har vi genom registerdata tagit reda på hur många personer som sökt sjukvård för Dupuytrens sjukdom i Skåne under en 16-års period (1998-2013), samt hur många som genomgått behandling och vilka metoder som använts. Utifrån dessa data har vi kunnat konstatera att cirka 1% av Skånes vuxna befolkning fått diagnosen av en läkare. Högst andel drabbade fann vi i gruppen män över 70 år, där nästan 5% fått diagnosen. Över hälften av de som fått diagnosen Dupuytrens sjukdom har genomgått behandling, där kirurgisk fasciektomi var den vanligaste behandlingsmetoden (87%). Ett trendbrott noterades 2013, då kollagenasinjektion användes i 40% av fallen, på bekostnad av minskat antal utförda kirurgiska ingrepp.

I *studie 2-5* har vi följt patienter som behandlats med kollagenasinjektion för Dupuytrens sjukdom. Vi har använt oss av en modifierad behandlingsmetod, där vi injicerar en högre dos av kollagenas i flera punkter i bindvävssträngen som orsakar fingerkontrakturen.

I *studie 2* har vi dokumenterat uppkomsten av sår i handflatan vid fingersträckningen och utvärderat det kortsiktiga behandlingsresultatet hos 146 patienter. I 40% av behandlade händer uppkom ett sår. Svår kontraktur innan behandling ökade risken för sår. Alla sår läkte komplikationsfritt och behövde ingen vidare kirurgisk behandling. Efter behandling minskade sträckdefekten i fingrarna avsevärt (medelvärde 55° förbättring).

I *studie 3* har vi undersökt om lokalbedövning kan minska behandlingssmärtan vid kollagenasinjektion. 187 patienter indelades i 3 grupper, där en grupp fick lokalbedövning innan kollagenasinjektion och 2 grupper fick kollagenasinjektion utan lokalbedövning (standard eller modifierad injektionsmetod). Patienterna som fick lokalbedövning innan kollagenasinjektion upplevde en minskad behandlingsrelaterad smärta (medelskillnad 2.1 på en 10-gradig skala). Den modifierade behandlingsmetoden var inte mer smärtsam än standardmetoden.

I *studie 4* utvärderades behandlingsresultaten 3 år efter behandling med kollagenasinjektion. 70% av behandlade fingrar hade ej drabbats av återfall. Bäst resultat uppnåddes vid behandling av knogledskontraktur, där 3 av 4 knogleder fortsatt var helt raka efter 3 år. Inga komplikationer rapporterades, och 70% av patienterna var mycket nöjda eller nöjda med behandlingen. Riskfaktorer för att drabbas av kontrakturåterfall var kontraktur i lillfingrets mellanled, tidigare

kirurgiskt ingrepp i det behandlade fingret samt avancerad kontraktur innan behandling.

I *studie 5* undersökte vi skillnaden i mätning av sträckdefekt i kontrakturdrabbade fingrar mellan 3 arbetsterapeuter, och kunde visa att skillnaden mellan aktiv och passiv sträckdefekt varierar signifikant mellan undersökare.

*Studie 6* är en pågående randomiserad klinisk prövning som jämför kirurgisk fasciektomi och kollagenasinjektion för patienter som drabbats av återfall i Dupuytrens sjukdom.

Sammanfattningsvis har avhandlingen påvisat att Dupuytrens sjukdom är en vanlig orsak till läkarkonsultation och att många drabbade genomgår behandling. Sjukdomens börda på sjukvården kommer troligtvis att öka i framtiden med tanke på en åldrande befolkning. Detta ställer krav på intensifierad forskning kring effektiva, säkra och kostnadseffektiva behandlingsmetoder för Dupuytrens sjukdom. Kollagenasinjektion har i avhandlingen visat sig vara en effektiv och säker behandlingsmetod som kan utföras på öppenvårdsmottagning. Sår i handflatan är vanligt vid fingersträckning, men läkningsprognosen är utmärkt. Lokalbedövning minskar patienternas behandlingsrelaterade smärta. Slutgiltigen fortsätter forskningen från denna avhandling med en klinisk prövning för att ta reda på hur man bäst behandlar de värst drabbade patienterna, de som får återfall i Dupuytrens sjukdom, och undersöker om kollagenasinjektionens goda egenskaper kan utnyttjas för denna patientgrupp.



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# Appendix

## Surgical fasciectomy in Skåne region

*Surgical fasciectomies in Skåne Region 2009- 2018 (121)*

3071 procedures

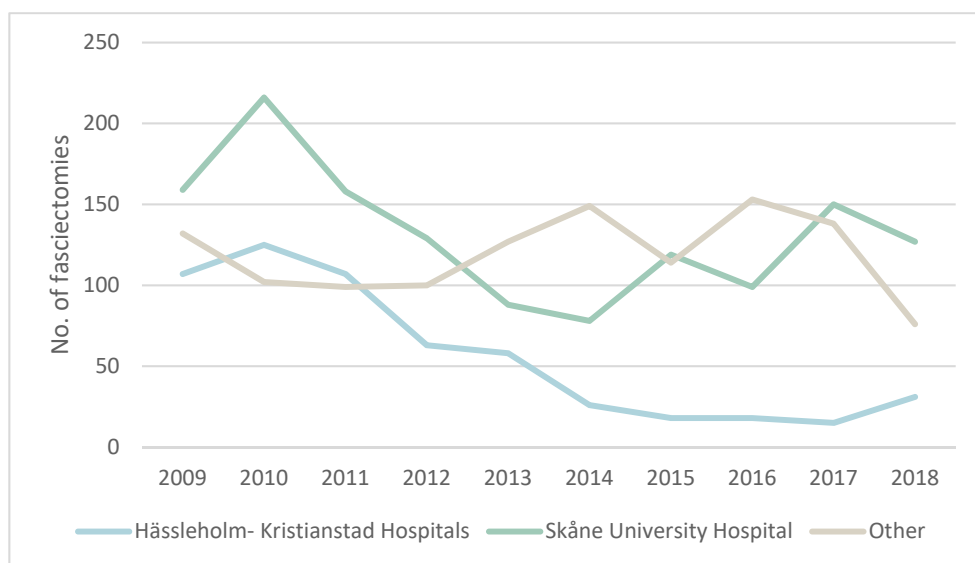
2975 day surgeries and 96 inpatient surgeries (only 2 inpatient surgeries 2018)

Procedures per treating facility (Figure 15):

Skåne University Hospital (the only hand surgery department) 1323

Hässleholm-Kristianstad Hospitals (the main study center of this thesis) 568

Other treating facilities (including private practice) 1190



**Figure 15. Dupuytren disease treatment trends in Region Skåne in Sweden 2009-2018 (the small increase in 2018 at Hässleholm-Kristianstad Hospitals related to ongoing randomized controlled trial)**

*Surgical fasciectomy at Hässleholm-Kristianstad Hospitals during the study period of Paper IV (November 2012 through June 2013)*

34 treated patients (34 hands)

Mean age 68 years (SD 8)

28 men (82%)

Reasons for choosing surgery (as stated in patient's electronic records):

Recurrence after previous	Surgical fasciectomy	6
	Needle fasciotomy	4
	Collagenase injection	1
Failed percutaneous needle fasciotomy		2
Severe proximal interphalangeal joint contracture		5
Patient's choice		5
Surgeon's preference (only performs surgery)		11

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