Dupuytren Disease

Treatment effect durability, recurrence, and patient-reported outcome measures

Eckerdal, David

2024

Document Version:
Publisher's PDF, also known as Version of record

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Printed by Media-Tryck, Lund 2024 NORDIC SWAN ECOLABEL 3041 0903

DAVID ECKERDAL is a specialist in orthopedic surgery at Hässleholm-Kristianstad Hospitals in southern Sweden. His thesis explores different aspects of Dupuytren disease, a common condition of the hand, that can lead to various activity limitations.

LUND UNIVERSITY

FACULTY OF MEDICINE

Department of Clinical Sciences
Orthopedics

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2024:155
ISBN 978-91-8021-652-4
ISSN 1652-8220

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David Eckerdal

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UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on December 20th at 13.00 in Rådhus Skåne, Kristianstad, Sweden

Faculty opponent
Marcus Sagerfors, Associate professor, Örebro University, Örebro, Sweden

Organization: LUND UNIVERSITY

Document name: Doctoral Dissertation **Date of issue** 24-12-20

Author David Eckerdal **Sponsoring organization**

Title and subtitle: Dupuytren Disease: Treatment effect durability, recurrence, and patient-reported outcome measures

Abstract

Purpose: To improve knowledge about Dupuytren disease, regarding treatment effect durability, recurrence and patient-reported outcomes.

Patients and methods: Paper I was a prospective cohort study investigating the 5-year outcomes regarding recurrence rates and risk factors for recurrence after collagenase injection. Paper II is a comparative cohort study comparing long-term outcomes after collagenase injection and surgical fasciectomy. Paper III is a systematic review evaluating the methodological quality and risk of bias in randomized controlled trials (RCTs) comparing collagenase injection with percutaneous needle fasciotomy (PNF). Paper IV is the 1-year results of an RCT comparing surgical fasciectomy with collagenase injection for recurrent Dupuytren disease. Paper V is a prospective cohort study comparing the short-term outcomes after collagenase injection using the Canadian Occupational Performance Measure (COPM). Finally, paper VI is the study protocol for an ongoing multicenter study aiming to develop a new Dupuytren-specific patient-reported outcome measure (PROM) using modern measurement methodology.

Results: Recurrence after collagenase injection occurred in 17% of metacarpophalangeal (MCP) joints and 25% of proximal interphalangeal (PIP) joints and a higher baseline joint contracture and treatment of the small finger were both risk factors for PIP joint recurrence. In the comparative cohort study, a joint contracture ≥20° was found in 25% of MCP and 33% of PIP joints after collagenase injections and 19% of MCP joints and 48% of PIP joints after surgical fasciectomy. All 5 RCTs included in the systematic review were found to have high risk of bias. There was no statistically significant difference regarding joint contracture between the 2 groups at 3-months and 1-year for patients randomized to surgical fasciectomy or collagenase injection for recurrent Dupuytren disease. The responsiveness for the COPM was high (Cohen's d, 2.6; 95% CI 1.9–3.3).

Conclusion: Five years after treatment with collagenase injection, 3 of 4 joints did not develop recurrence. Patients treated with collagenase and surgical fasciectomy show significantly better joint contractures at 5 years compared to baseline but joint contractures ≥20° are common. Risk of bias was high in published RCTs comparing collagenase injection with PNF. When treating recurrent disease, the short-term (3-month and 1-year) outcomes were similar after surgical fasciectomy and collagenase but collagenase-treated patients had significantly less activity limitations up to 6 weeks after treatment and fewer complications. The COPM demonstrated 4-times higher responsiveness than the QuickDASH. The development of a new valid Dupuytren-specific PROM will contribute to improved Dupuytren research in the future.

Key words: Dupuytren disease, Dupuytren contracture, Recurrence, Outcome measures, surgical fasciectomy, collagenase

Classification system and/or index terms (if any) Supplementary bibliographical information

Language: English **ISSN** 1652-8220

ISBN: 978-91-8021-652-4

Recipient's notes **Number of pages**: 82

Price Security classification

Signature Date 2024-12-20

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ISBN 978-91-8021-652-4
ISSN 1652-8220

Printed in Sweden by Media-Tryck, Lund University
Lund 2024

To my family and friends

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List of Papers

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. **Eckerdal D**, Lauritzson A, Åkesson A, Atroshi I. Risk factors for long-term contracture recurrence after collagenase injection for Dupuytren disease: a prospective cohort study. Biomedicines, 2023;11(3):699.

II. **Eckerdal D,** Lauritzson A, Nordenskjöld J, Åkesson A, Atroshi I. Finger joint contractures 5 years after treatment for Dupuytren disease: a comparative cohort study of collagenase injection versus surgical fasciectomy. Journal of Hand Surgery American volume, 2022;47(9):834-842.

III. **Eckerdal D**, Pakosta H, Ali M, Atroshi I. Bias in published randomized trials that compare collagenase injection with percutaneous needle fasciotomy in the treatment of Dupuytren disease: a systematic review. EFORT Open Reviews, 2024;9(7):625-631.

IV. **Eckerdal D**, Nordenskjöld J, Lauritzson A, Kopylov P, Atroshi I. Surgical fasciectomy versus collagenase injection in recurrent Dupuytren disease: 12-week and 1-year results of a randomized controlled trial. *Manuscript*.

V. Lauritzson A, **Eckerdal D**, Atroshi I. Responsiveness of the patient-specific Canadian occupational performance measure and a fixed-items activity limitations measure in patients with Dupuytren disease. Journal of Patient Reported Outcomes, 2023;7(1):38.

VI. **Eckerdal D**, Lyrén PE, McEachan J, Lauritzson A, Nordenskjöld J, Atroshi I. Development of a new patient-reported outcome measure for Dupuytren disease: a study protocol. Health Informatics Journal, 2024;30(4).

Abbreviations

AE	Adverse event
AED	Active extension deficit
CI	Confidence interval
CISSS	Cold intolerance symptom severity scale
COPM	Canadian occupational performance measure
CTT	Classical test theory
DASH	Disabilities of the arm, shoulder, and hand
EQ5D	EuroQol 5-dimensions
IRT	Item response theory
MCP	Metacarpophalangeal
OR	Odds ratio
PED	Passive extension deficit
PEM	Patient evaluation measure
PIP	Proximal interphalangeal
PNF	Percutaneous needle fasciotomy
PROM	Patient-reported outcome measure
QuickDASH	Quick disabilities of the arm, shoulder and hand
ROM	Range of motion
SD	Standard deviation
SDSS	Southampton Dupuytren scoring scheme
TAED	Total active extension deficit
TPED	Total passive extension deficit
URAM	Unité Rhumatologique des Affections de la Main
VAS	Visual Analog Scale

Chapter 1: Background

1.1: Introduction

Believed to have been described as early as around 1200 AD in Icelandic sagas [1], Dupuytren disease is a common fibroproliferative disease presenting with thickening of the palmar fascia, simple nodules, and sometimes rigid cords in the palm (Figure 1). While many patients are asymptomatic, Dupuytren disease can develop in a more aggressive form in which the cords contract, resulting in flexion contractures of the fingers [2]. When flexion contractures have developed, these contractures can impact functional use of the hand and limit a wide array of daily activities such as self-care, shaking hands, donning gloves or participating in sports and hobbies [3].

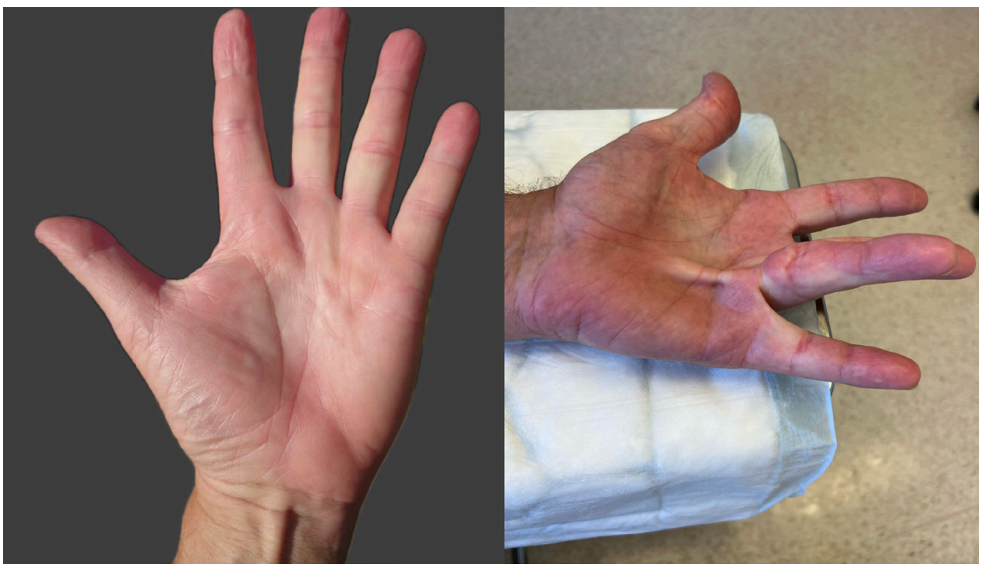


Figure 1. Different stages of Dupuytren disease from barely noticeable nodules along the 4th ray (left) to established contracture (right)

Despite bearing his name, the first medical description of Dupuytren disease was not provided by baron Guillaume Dupuytren [1, 4, 5]. Finger contractures were described in the early 17th century by Felix Plater and in the 18th century Henry Cline described the involvement of the palmar fascia and suggested fasciotomy as treatment [1, 5, 6]. Baron Guillaume Dupuytren further advanced the knowledge and reported on the disease and surgical fasciotomy during a lecture at Hotel-Dieu 1831. Transcribed by his assistants, the lecture was later translated to English and published in the Lancet in 1834 [7]. The first surgical fasciectomy was then performed in the mid 19th century by Sir William Fergusson (after the introduction of anesthesia) [8]. In the following one and a half century treatment trends have gone from less invasive to more radical treatments and back again [5, 9]. Today most patients are treated either with percutaneous needle fasciotomy (PNF), or with a pharmacological treatment using Collagenase Clostridium Histolyticum injection, or with surgical fasciectomy which has been considered gold standard [10]. Collagenase was introduced in 2010 and its introduction resulted both in a new treatment option and also in renewed interest in Dupuytren disease and Dupuytren research. This has resulted in several studies evaluating and comparing treatment methods. Both with regard to objective outcome measures and patient-reported outcome measures (PROMs) to capture the patients' subjective opinion.

Despite that Dupuytren disease was described several centuries ago, much is still unknown and there is a continuous debate regarding superiority of different treatments. This thesis will try to increase the knowledge about Dupuytren disease, focusing mainly on the long-term outcomes after different treatment modalities and patient-reported outcome measures used in Dupuytren research as well as the development of a novel PROM to be used in future Dupuytren research.

1.2: Pathophysiology

While Dupuytren disease has been treated for more than three centuries, it is only in the last decades that the mechanisms behind the disease have started to unravel. The initial theory proposed by Dupuytren among others, was that Dupuytren disease developed as response to trauma [11]. In recent years it has been established that genetic factors play a significant role, but much is still to be uncovered. What has been established is that myofibroblasts with the ability to contract and produce collagen play a significant part in the pathogenesis of Dupuytren disease, both in the formation of nodules and potential contracture [12, 13].

Heredity is often described as the main factor affecting disease progression in Dupuytren disease. To this date there is no single responsible gene isolated and it has still not been established whether Dupuytren disease is a monogenic or an oligogenic disorder [14]. Epidemiological studies have shown differences in

prevalence between regions that could be a result of either genetics, environmental factors or both [15]. Furthermore, in a study by Ling et al. examining the families of 50 patients with Dupuytren disease a strong familiar occurrence was shown [16]. It has also been established that patients with heredity for Dupuytren disease may present earlier and with more aggressive disease [17]. While the role of heredity is still under debate, multiple genes affecting the disease development and severity have been identified through genome-wide association studies [18].

Hopefully, some of these genes may be targeted in future treatments to stop disease progression in an early phase [18].

1.3: The normal and pathological anatomy of the palm and fingers

When trying to understand Dupuytren disease, knowledge of the normal anatomy of the hand is crucial since Dupuytren disease progresses along the normal anatomical structures of the hand (Figure 2). The palmar aponeurosis (or fascia) is a strong fascial membrane that covers and protects the muscles and flexor tendons in the palm while it also anchors the skin to improve the grip. Originating from the palmaris longus tendon, (or from the flexor retinaculum in the wrist, when no palmaris longus tendon is present) the palmar fascia extends distally, dividing into pretendinous bands following the metacarpals. At the distal end of the metacarpal the pretendinous bands divide and form a superficial layer that attaches to the skin, and a central layer that form 2 spiral bands extending distally and dorsally. Finally, a deep layer that extends vertically terminating at the interosseus fascia and the deep transverse metacarpal ligaments, thus forming the septa of Legueu and Juvara. The transverse ligament extends deep and transverse from the pretendinous bands located proximally to their division, while the natatory ligament also runs transversely but distally to the division of the pretendinous bands. The septa of Legueu and Juvara, the spiral bands and the natatory ligament then join each other in the web space coalescence, forming the lateral digital sheet. While the lateral digital sheet runs in the sagittal plane, there are also transverse fibers. These run volar and dorsal to the neurovascular bundle forming Grayson's and Cleland's ligaments respectively [8].

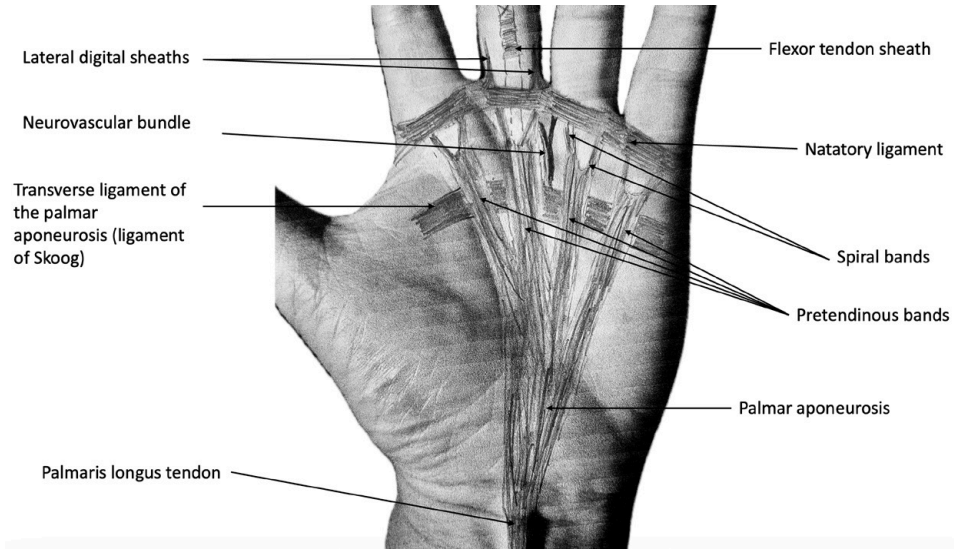


Figure 2. Overview of the normal anatomy of the palmar fascia of the hand

The pathological changes in Dupuytren disease often begin with the formation of nodules distally along the pretendinous band. When the superficial layer attaching to the skin starts to contract this results in the formation of pits between the MCP joint and the distal palmar crease. If the disease progresses beyond this point, the pretendinous band is the subsequent structure to be affected, resulting in a pretendinous cord and MCP joint contracture. Dupuytren disease then progresses by affecting the spiral bands, Grayson's ligament and the lateral digital sheet which together make up the spiral cords that may displace the neurovascular bundles (thus complicating surgery). Distal to the spiral cords, the lateral digital sheet can also progress into lateral cords. There are also digital cords originating distal to the MCP joint causing PIP joint contracture, as well as natatory cords, originating from the natatory bands, that limit finger abduction and contribute to PIP contracture [8].

1.4: Epidemiology

With a reported prevalence ranging from 0.6% to 32% in western countries Dupuytren disease is often referred to as the "Viking's disease" [19]. However, while popular among patients, the concept of Dupuytren disease being a disease of the Vikings has been questioned in recent years. While not all Vikings were of Norse origin, a genetic study did not find any evidence of a Norse origin of Dupuytren disease [20]. In a more recent genetic study, Ågren et al. found that Neanderthal inheritance is associated with Dupuytren disease [21]. Furthermore, a systematic

review published in 2020, including 85 studies, estimated the global prevalence of Dupuytren disease as 8% and interestingly, the highest prevalence (17%) was reported in South Africa [22]. However, the prevalence in South Africa was based on only 2 studies, 1 investigating hand conditions in a diabetic population and 1 investigating hand conditions in 111 adults from an island which at that time held a population of less than 300 [23, 24].

When discussing the prevalence of Dupuytren disease it is important to remember that the manifestation of the disease may vary and subsequently, the prevalence may vary depending on the definition of the disease. In a study by Lanting et al. the prevalence of Dupuytren disease in the Netherlands was 22% in the study population, but less than a fifth of these had contractures [25]. As patients without contractures may not have any disability or symptoms of their Dupuytren disease, it is reasonable to believe that a large number of patients with Dupuytren disease may not seek medical advice. This is further highlighted in another study in which the prevalence of Dupuytren disease, diagnosed by a medical doctor at a health care facility, in a general population in southern Sweden was only 0.92% [26]. Still, regardless of which definition of disease is used, it is obvious that Dupuytren disease is common in the general population and the need for more knowledge is crucial. Especially since the incidence and prevalence appear to be increasing [27].

1.5: Risk factors

Moving on from epidemiology this thesis continues with a short summary of the many risk factors for Dupuytren disease. Probably of most importance is the Dupuytren diathesis, defined by Hueston et al. in 1963 as factors that may predict a disease that is more severe or prone to recur after treatment. The original Dupuytren diathesis as described by Hueston included familial history of Dupuytren disease, bilateral disease, ethnicity and ectopic disease (Dupuytren disease found in other locations than the palmar fascia) [28]. Modified in 2006 the Dupuytren diathesis now also include 2 additional risk factors; male gender and age <50 years at onset as well as ectopic disease has been modified to only include knuckle pads, and it has been estimated that patients with all the risk factors have an increased risk of recurrence by 71% [29].

In addition to the Dupuytren diathesis several other risk factors have been considered. Suggested already by Baron Dupuytren the perhaps most obvious of these risk factors is trauma (such as previous surgery, repetitive use [manual labor, hobbies, sports] or hand injuries) [30-33]. Furthermore, a relationship has been shown between both smoking and alcohol consumption and Dupuytren disease, but smoking does not seem to affect treatment outcome [34-38]. Adhesive capsulitis (frozen shoulder) is histologically similar and strongly correlated to Dupuytren

disease [39, 40]. Diabetes is perhaps the most well-known condition to be connected to Dupuytren disease which is considered as part of the "diabetic hand" [41]. A relationship has also been shown with liver disease, epilepsy, and hypertension among others [42, 43]. Interestingly, high BMI as well as rheumatoid arthritis seem to decrease the risk of Dupuytren disease, suggesting perhaps a protective genetic or immunological factor [44-46].

1.6: Outcome assessment

One of the main issues in Dupuytren research is the inconsistency in the assessment of outcome, making comparative reviews difficult or impossible to perform [47, 48]. Most studies report clinical measurements such as range of motion or recurrence as outcomes, but patient-reported outcomes are gaining popularity. However, even within these categories there is a large heterogenicity between different studies.

Range of motion

The most commonly used outcome measure is range of motion (ROM) [47, 48]. For Dupuytren disease, extension deficit is the standard method to report ROM and can be reported either separately for the MCP and PIP joints, and when necessary for the distal interphalangeal joint, or as total (MCP+PIP) extension deficit. Passive extension deficit (PED) (Figure 3), theoretically representing the best possible extension in fingers affected by Dupuytren disease, has typically been used in studies [49-52]. However, in recent years, active extension deficit (AED), which represents the patient's functional ROM, has been gaining popularity [53-55]. To date it has still not been agreed upon whether PED or AED is superior, but it has been suggested that a larger issue is that many studies do not report which one they have measured [9, 56]. Also, despite that ROM is an objective outcome measure it does not always correlate with patients' activity limitations, and it has been shown that measurement of ROM differs between assessors [54, 57, 58].

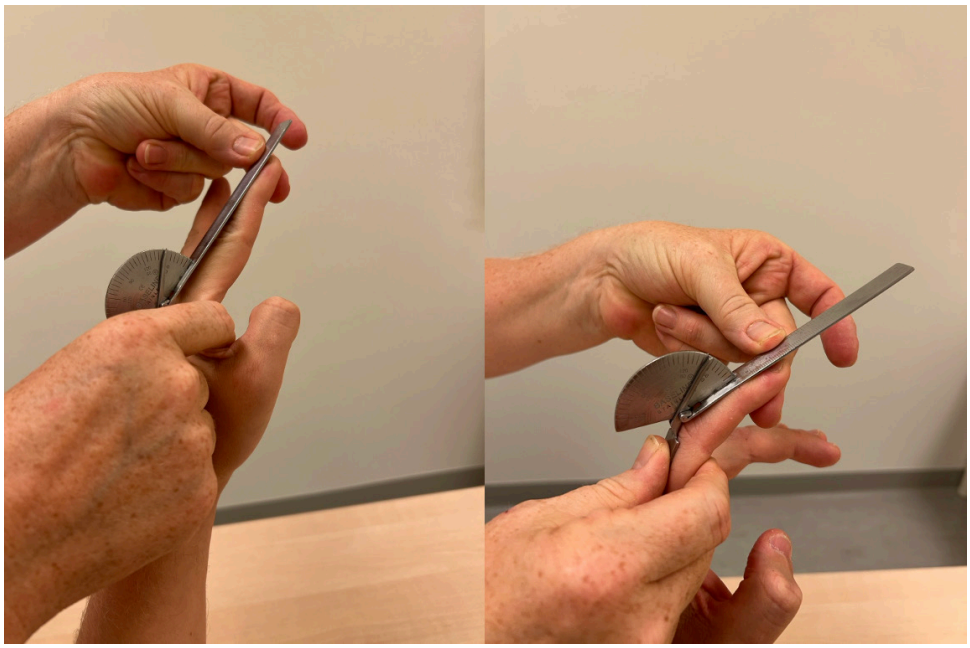


Figure 3. Measurement of passive extension deficit of MCP and PIP joints

Recurrence

Recurrence is another frequently used outcome measure in Dupuytren research. While in theory recurrence is a definite and appealing outcome measure, recurrence has proved difficult to define. In different studies the definition of recurrence ranges from any signs of Dupuytren disease, e.g., a palpable nodule in the palm, to a contracture of 20° in a treated joint, and to a worsening in joint contracture between early post-treatment measurements and an endpoint [9, 52, 59]. The difference in the definition of recurrence has also been identified in a review as an explanation of the large difference in recurrence rates ranging from 0% to 100% in different studies [60]. To address this issue and allow better comparability between studies an expert group used the Delphi method to develop a definition of recurrence to be used in clinical studies. They suggested that recurrence should be defined as loss of extension in a treated joint by ≥20° between early (6 weeks) postoperative measurements and (to simplify clinical studies) 1 year after treatment [61]. Another Delphi group study suggested a similar definition of loss of passive extension (PED) in a treated joint by ≥20° between early (6 to 12 weeks) postoperative measurements and a later (unspecified) time point [62].

Patient-reported outcome measures

To address the patient's subjective opinion of their treatment outcome, PROMs are often used in studies. As with other outcome measures there is also a heterogenicity in PROMs in Dupuytren research [47, 48]. Fixed-item PROMs (PROMs with fixed questions in contrast to the adaptive questions of patient-specific PROMs) are often used. The Disabilities of the Arm, Shoulder, and Hand (DASH), or its short form the QuickDASH, has been the most used PROM in Dupuytren research [54, 63]. Two disease-specific PROMs, the Southampton Dupuytren Scoring Scheme (SDSS) and the Unité Rhumatologique des Affections de la Main (URAM) have been developed with the aim to be more specific than upper-extremity PROMs such as the DASH [64, 65]. Patient-specific outcome measures such as the Canadian Occupational Performance Measure (COPM) can also be used in Dupuytren research to account for the fact that fixed-item PROMs may not capture the wide array of activity limitations experienced by Dupuytren patients [63, 66]. Below follows a brief description of some of the PROMs that are commonly used in Dupuytren research and are relevant for this thesis. Some PROMs such as the COPM will be more thoroughly described later in *Paper V.* However, it is obvious that there is need for a responsive PROM that is easy to administer and use both in future research and clinical practice. The process of designing a novel PROM will be presented in *Paper VI.*

Brief description of some of the PROMs commonly used for Dupuytren disease or that are referred to in the papers included in this thesis.

- Canadian Occupational Performance Measure: The COPM is a patient-specific outcome measure allowing patients to identify and rate their performance in specific tasks of their own choosing [67]. The COPM is performed as a semi-structured interview in which the interviewer asks the patient to identify and list up to 5 activities and categorize them into either self-care, productivity or leisure. The patients then rate their performance with each activity from 1 (worst) to 10 (best) and then rate their satisfaction with how they perform the activity. The interviewer records the patients' responses and at follow-up the patients rate their performance and satisfaction with the same activities [67]. In *paper V* of this thesis the COPM will be more thoroughly described.
- Cold Intolerance Symptom Severity Score (CISSS): The CISSS is a PROM with a score range from 4 (best) to 100 (worst) that measure the cold intolerance of an affected hand and effects of cold intolerance on daily activities [68].
- Disabilities of the Arm, Shoulder and Hand (DASH)/QuickDASH: The 30-item DASH or its short form, the 11-item QuickDASH, is an upper-

extremity fixed-items PROM. The scale score ranges from 0 (best) to 100 (worst) and the DASH/QuickDASH was the most commonly used PROM in Dupuytren disease according to a systematic review published in 2013 [47]. As a general upper extremity PROM, the DASH/QuickDASH may not cover all relevant aspects of Dupuytren disease while some items may not be relevant. The QuickDASH has been shown to be an acceptable PROM for Dupuytren disease [69]. However, the key criticism has been that the QuickDASH score does not correlate with the extension deficit [69, 70]. The DASH and QuickDASH also include questions regarding pain. Pain has been a topic of debate because although Dupuytren disease is usually described as painless, some patients do experience pain and pain is also an important aspect of the early postoperative phase [63, 71].

- EuroQol 5-Dimensions (EQ5D): While neither an upper extremity PROM nor a Dupuytren PROM the EQ5D is commonly used in health care. With a score scale ranging from -0.594 (worst) to 1.0 (best) the EQ5D index measures health related quality of life in 5 dimensions, mobility, self-care, usual activities, pain/discomfort and anxiety/depression [72].
- Palmar Pain Scale: This is a hand-specific PROM with a score range from 0 (best) to 100 (worst) consisting of 2 items measuring pain in the palm and its effect on daily activities [73].
- Patient Evaluation Measure (PEM): The PEM is a hand-specific PROM originally validated in patients with scaphoid fractures, with a scale score ranging from 0 (best) to 100 (worst) [74].
- Southampton Dupuytren Scoring Scheme: The SDSS was developed as a Dupuytren-specific PROM, consisting of five items with a scale score ranging from 0 (best) to 20 (worst) [65]. The items included in the SDSS mainly assess activity domains rather than specific activities. Similar to the DASH and QuickDASH the SDSS has not demonstrated strong correlation with the degree of extension deficit and, despite being disease-specific, the SDSS does not seem to perform better than hand-specific PROMs [65, 75].
- The Unité Rhumatologique des Affections de la Main: The URAM consists of 9 items and was, like the SDSS, developed as a Dupuytren-specific PROM with scale score ranging from 0 (best) to 45 (worst) [64]. Since its development, URAM has been used in several Dupuytren studies including RCTs [50, 51]. The URAM has been shown to be a responsive PROM that correlates with severity of contracture [76, 77]. However, the URAM does not include typical Dupuytrens-related activities such as donning gloves and its relevance has been questioned [63, 64].

Classical test theory and item response theory

A common aspect for the PROMs used in Dupuytren research is that they were mostly developed using conventional methodology based on classical test theory (CTT). The assumption in CTT is that all test takers have a true score and that their final or observed score on a test is made up by their true score plus a random error [78]. There are however limitations with CTT, such as that both the random error is dependent on the test taker and that the item difficulty is dependent on the test [78]. Thus, an easier test may overestimate the knowledge of the test taker and vice versa. Item response theory (IRT) is a modern method for developing and evaluating tests. IRT has previously been used when evaluating educational tests and can be used to describe the relationship between the characteristics or skill of independent test takers and their responses to specific items [79]. IRT is based on different assumptions. The primary assumption is that latent variables, such as the skill or knowledge, affects the test taker's answers to a test and the items also have different characteristics such as item difficulty. Through different statistical models, IRT can be used to analyze the probability that a test taker with a certain latent ability or skill answers correctly on a specific item. [79] IRT has several benefits compared to CTT including that in difference to CTT, the provided scores are independent of the items. Thus, the test taker score should be constant irrespective of test difficulty [79]. The IRT models also provide information regarding each item which is useful in PROM development and IRT can also be used to better design a PROM for the intended patient group [79, 80].

1.7: Treatment

Throughout the years several different treatments have been utilized to treat Dupuytren disease but there is still no cure. Thus, all current treatments aim to reduce contractures and improve hand function for as long as possible. In 1999, Tubiana defined the characteristics of an optimal treatment for Dupuytren disease as correcting contracture, avoiding complications and short recovery while preventing recurrences [81]. 25 years later the optimal treatment for Dupuytren disease is yet to be discovered [9].

As Dupuytren disease is not dangerous, it is the loss of function that constitutes indication for treatment. Hence, as patients differ in their demands, there is no defined threshold for when Dupuytren disease needs to be treated. However, a contracture of 30° in an affected joint is often considered a threshold for more invasive treatment [9]. A 30° contracture also correlates well with a positive "Table top test" (Figure 4) as described by Hueston and can be used as a simple test that is easy to perform when patients present with limitations in their daily activities [82].

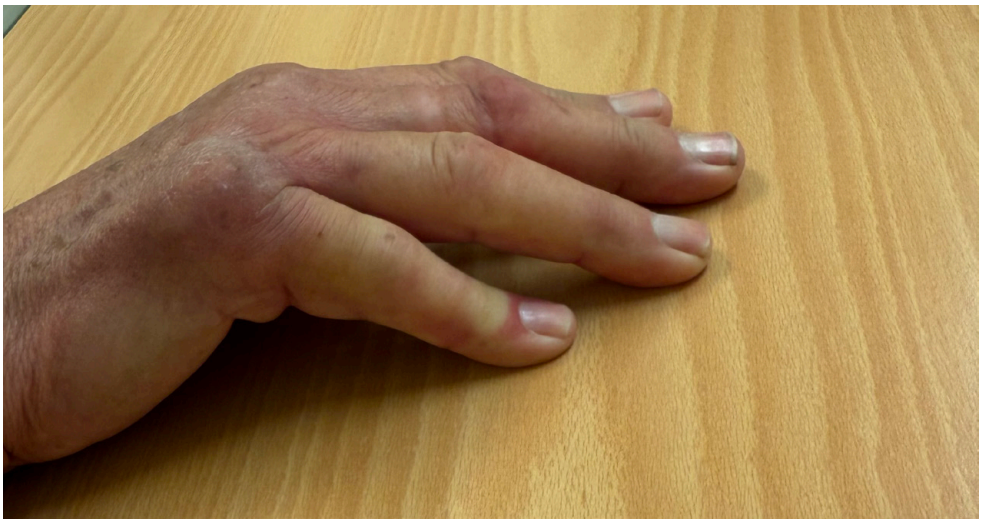


Figure 4. Positive table top test performed by a patient with Dupuytren disease

The following section will present some of the most common treatments for Dupuytren disease. For simplicity and due to its relative invasive nature, collagenase injection is included in the surgical group.

Non-surgical treatments

An optimal treatment for Dupuytren disease would prevent or delay disease progress in an early phase of the disease before the development of contractures and limitation of hand function. Thus, several early-stage non-surgical treatments in Dupuytren disease have been evaluated, some of which are presented below. However, the studies evaluating these methods are generally poorly designed and the evidence is lacking [83, 84].

Observation

Due to the benign and typically slowly progressive nature of Dupuytren disease active expectancy is often a viable option for patients with low or no disability.

Physiotherapy and splinting

Different physiotherapy interventions including splinting and stretching have shown improvement in contracture, but the studies are generally small, and evidence is limited [83, 85].

Radiation

Low-dose radiation has been suggested as a non-surgical treatment to delay disease progression in early Dupuytren disease. While the exact mechanism is still uncertain, the hypothesis is that radiation may affect disease progression by halting the development of fibroblasts in the fascia [86, 87]. However, as shown in a systematic review, the evidence supporting the use of radiation in treating Dupuytren disease is weak [88]. Furthermore, the risk that radiation may increase future surgical complications as well as the ethical considerations regarding a potentially toxic treatment as means of delaying a benign condition should also be taken into consideration [86].

Pharmacological treatments

Several pharmacological treatments have been tried for Dupuytren disease. Degreef et al. reported promising yet transient short-term effects of high-dose tamoxifen as a neoadjuvant treatment [89]. Corticosteroids have also been suggested as a possible treatment for Dupuytren disease, based on the theory of inflammation preceding fibrosis, however the evidence is lacking [83, 84, 90]. In recent years Tumor Necrosis Factor (TNF) has been identified as a potential drug target as TNF-β is involved in the activation of myofibroblasts [91]. While no drugs are available in clinical practice a recent Phase 2b study with intra-nodular injections of Adalimumab (an anti-TNF therapy) resulted in nodules softening and decreasing in size [91]. These findings may indicate that biological treatments for Dupuytren disease may be possible in the future.

Surgical treatments

Open surgery

While open surgery has been the main treatment for Dupuytren disease during the last century, the extent has varied and today limited fasciectomy (sometimes referred to as surgical fasciectomy) is the most common treatment [92]. Surgical fasciectomy has traditionally been performed in an operating room under tourniquet control, but in recent years Wide-Awake Local Anesthetic No Torniquet (WALANT) has gained popularity. The rationale of the surgical fasciectomy (Figure 5) is straightening of the affected digit through the removal of Dupuytren cords and nodules, while the neurovascular cords are identified and protected. Numerous types of skin incisions can be used but typically a Brunner (zigzag) or straight incisions combined with Z-plasties are used. When needed the fasciectomy can be supplemented with additional procedures such as PIP capsulotomy or checkrein ligament release to correct severe PIP joint contractures. Skin incisions are sutured, and potential skin deficits are either left to heal by secondary intent or covered by a skin graft. Soft dressings are typically used but can be supplemented

by a cast and sometimes pinning of the joint. Hand therapy is typically initiated in the early postoperative phase and despite lack of scientific evidence, night splinting is often recommended [93, 94].

Surgical fasciectomy is effective for both primary and recurrent contractures of varying severity in all affected joints, and treatment outcomes are generally good. The reported recurrence rates range from 12% to 73%. However, complications are common, occurring in up to almost 40% of the patients [59, 86, 95-98]. Also, the postoperative recovery time is longer than after minimal invasive treatments [99]. Complications typically include delayed wound healing, infection, injuries to the digital nerves or arteries and complex regional pain syndrome. When treating recurrent contractures, the complication rates are typically higher due to the presence of scarring and changes in the normal anatomy [95]. Surgical fasciectomy is also often associated with the highest procedure costs as surgical fasciectomy is performed in an operating room, thus requiring more material and resources in combination with a longer rehabilitation time and sick leave [99, 100]. However, for patients with severe contractures that may be difficult to address with other treatment options, or with previous fast recurrences, fasciectomy may still be the most cost-effective option [100].

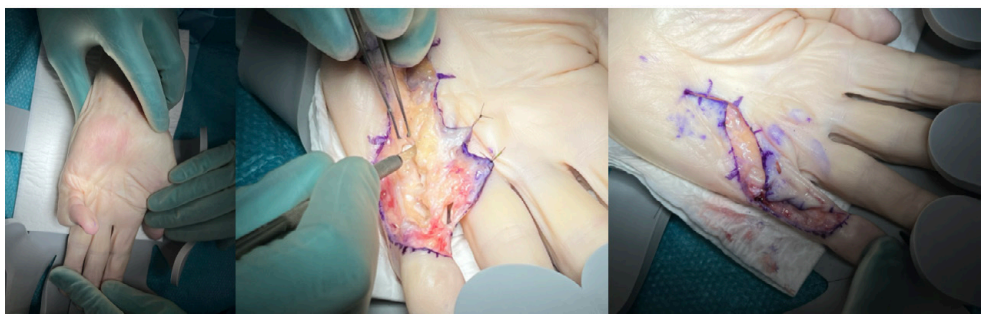


Figure 5. Surgical fasciectomy

Percutaneous Needle Fasciotomy

Gaining popularity in the last 20 years PNF is a minimally invasive treatment allowing treatment of contractures in the office setting. PNF is suitable for cooperative patients with a contracture caused by a palpable cord. Since the cords are insensate, only the skin needs to be anesthetized. There are different techniques for PNF. In the method as described by Eaton, division of the cord (after intradermal administration of local anesthesia [LA]) is performed at multiple sites in 3 different steps using 25-gauge needles (Figure 6) [101].

- First, the needle is used to separate the skin from the underlying Dupuytren cord.
- Second, the cord is weakened through multiple perforations by the needle.
- Last, through a sweeping motion the needle divides the cord, thus allowing straightening of the finger.

As the Dupuytren cords are situated adjacent to both the neurovascular cords and the flexor tendons, patient cooperation is crucial by flexing or extending fingers as well as alerting the surgeon of any pain or tingling in the fingers. If skin ruptures occur, postoperative care includes standard wound care. Otherwise, the patient typically receives a minor soft dressing and is advised to avoid firm gripping during the first week but is allowed to immediately commence with other activities and hand therapy [101].

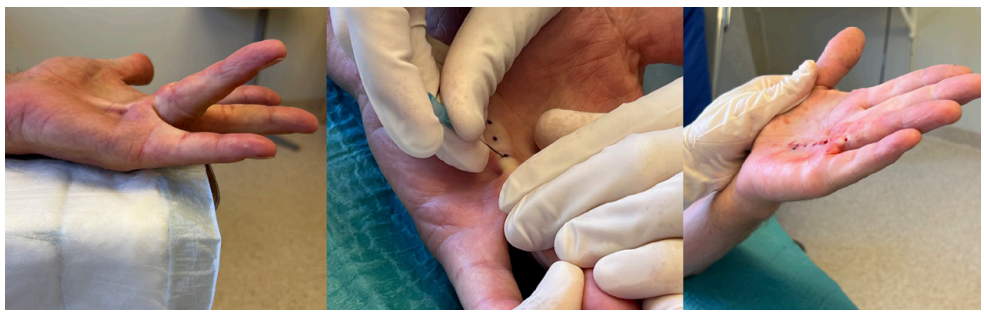


Figure 6. Percutaneous needle fasciotomy

PNF has been shown to be effective in reducing contractures especially for MCP joints with a low rate of complications, mostly skin tears [102-104]. Because PNF can be performed in 1 session in an office setting with minimal material required, it is associated with low costs, which is often highlighted as an advantage of the method [51]. However, the simplicity of the method also comes with a price as it is associated with high recurrence rate [97, 105]. It has been suggested that repeated corticosteroid injections can result in lower TAED for as long as 2 years after PNF [106].

Collagenase injection

Following the publication of the Collagenase Option for Reduction of Dupuytren's (CORD) study in 2009, treatment using injectable Collagenase Clostridium Histolyticum (Figure 7) was introduced and can (similar to PNF) be performed in the office setting [49]. Collagenase weakens the Dupuytren cords through lysis allowing it to be ruptured during the following manipulation (forced extension) [107]. In the original method 0.58 mg of collagenase was reconstituted with sterile

diluent and injected into a single cord, followed by finger manipulation the following day [49]. The method has since been modified and 1 or 2 vials of approximately 0.8 mg per vial can be injected in multiple sites of the Dupuytren cords to correct contractures in multiple fingers and joints [108-110]. Today the use of local anesthesia for both injection and manipulation is considered standard, and delayed extension up to 7 days after injection has been shown to be safe and effective [111-114]. Like PNF the care after injection and manipulation is simple and includes standard wound care in case of skin ruptures, soft dressings, and hand therapy. Similar to surgical fasciectomy a night orthosis is often used after treatment but has not shown to provide any beneficial effect [115].

Similar to PNF, the most obvious advantage of collagenase is the possibility to treat patients in an office setting with a short recovery time. However, 96.6% of patients in the initial CORD-study experienced at least 1 complication and recent RCTs have suggested that adverse events are more common after collagenase than after PNF [49, 52]. It has been suggested that the typical transient local effects of collagenase such as swelling, pain and bruising should not be considered as adverse events of treatment and the authors of one RCT did not include these as adverse events [50].

While collagenase injections are still used by surgeons in the USA [116], it was withdrawn from other markets in 2020 due to marketing reasons. Thus, surgical fasciectomy and PNF are the only currently available treatments outside the USA.

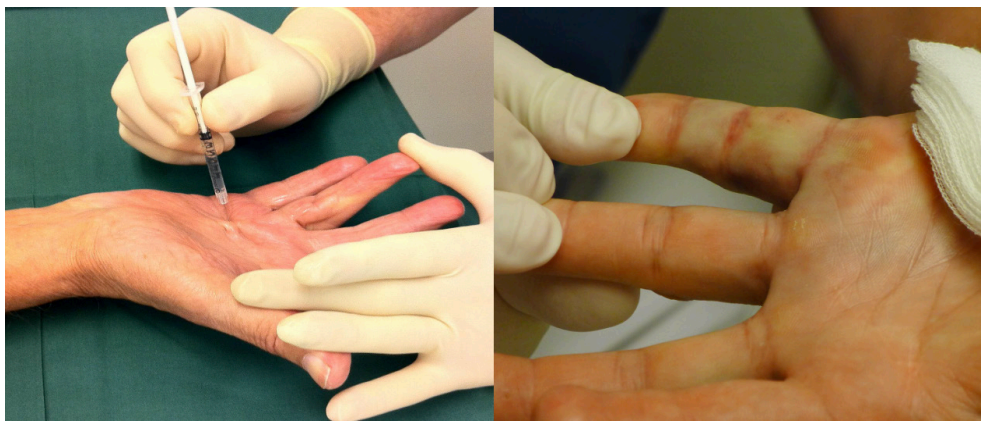


Figure 7. Collagenase injection (left) and finger extension (right)

Treatment of recurrent disease and salvage procedures

When discussing treatment of recurrent disease, it is important to establish that recurrences differ between patients. For instance, treatment of patients previously treated with surgical fasciectomy may be complicated due to scarring or skin defects while recurrences after PNF have been reported to be less complicated [117, 118].

The impact of collagenase on future surgical fasciectomy is still unclear with few studies published. It has been suggested that collagenase may contribute to scarring and distortion of the normal anatomy, but a recent study reported low complications for subsequent fasciectomy after collagenase [119, 120].

There is no consensus regarding optimal treatment for recurrent disease, and there have been no published RCTs comparing treatment options for recurrent disease. However, a recent review established that there is low-level evidence for surgical treatments such as surgical fasciectomy but also for PNF and collagenase [121].

Surgical fasciectomy is still considered gold standard for treating recurrent disease. Advantages of surgical fasciectomy include the possibility for surgeons to manage scarring or defects of the skin and combine the fasciectomy with additional procedures (e.g., PIP joint capsulotomy or checkrein ligament release) to treat stiff PIP joints [122]. Despite good contracture reduction, a higher risk of complications has been reported when treating recurrent disease. For instance, the risk of injury to digital nerves or arteries when treating recurrent disease has been reported to be ten times higher than that for primary disease [95, 118, 121, 123].

Following the increased popularity of minimal invasive treatments during the last decades both collagenase and needle fasciotomy have been utilized to treat recurrent contracture, though there are few studies evaluating their effect [117, 118]. PNF has been evaluated for recurrent disease by van Rijssen et al. and by Molenkamp, with satisfactory outcomes reported, but the studies only included 30 and 21 patients respectively [117, 124]. A more recent study also reported satisfactory outcomes for repeated PNF, yet with a trend of decreasing time between treatments for each new treatment [125]. For collagenase there are few available studies on treatment for recurrent disease. The studies that exist do however seem to support that collagenase can be utilized for recurrent disease after previous surgical and collagenase treatments with satisfactory result [59, 126-128].

Salvage procedures can be a valid option for patients with complex recurrent contractures with significant scarring or previous complications. For patients with maintained neurovascular function but severe PIP joint contracture, arthrodesis can give satisfactory outcome and can be supplemented with surgical fasciectomy. Partial or complete digital amputation is often reserved for patients who have had several previous fasciectomy procedures and with neurovascular dysfunction [122]. Despite traditionally considered a salvage procedure, amputations due to Dupuytren disease are not uncommon. It has been reported that 39% of elective digital amputations were due to Dupuytren disease, and amputations have been reported to represent almost 2% of all Dupuytren procedures [26, 129]. In recent years new procedures involving middle phalanx resection with or without collateral ligament reconstruction and middle phalanx resection with proximal to distal phalanx arthrodesis have also shown promising results but are still considered experimental [130-132].

Comparison of treatment methods

Surgical fasciectomy, PNF and collagenase are today the most common treatments for Dupuytren disease [133]. RCTs are considered gold standard when comparing treatment modalities [134]. While previous studies have compared 2 treatments with each other, a recently published RCT by Räisänen et al. is the only published study comparing the three common treatment methods [135]. In that study with a 2-year follow-up, the 3-month success rate (defined as contracture reduction of >50% and that patients were satisfied with outcome and have no interest in further treatment provided that their functional impairment does not worsen) was similar for the 3 treatments [135]. Also, as in previous studies comparing PNF with fasciectomy, the long-term outcomes (2 years) were better maintained for surgical fasciectomy than for PNF and collagenase [97, 135, 136]. However, there was a difference regarding the follow-up time as the 2-year follow-up for the surgical group was based on the date of recruitment and not the date of surgery. As PNF and collagenase were typically performed on the day of inclusion the time interval from treatment to the 2-year follow-up was shorter for the surgical group. Still, an interesting finding in the study is that the long-term outcomes (2 years) were better for collagenase than for PNF, though the difference was small, and differences in treatment costs and side effects need to be taken into account [135]. Finally, as in previous studies, serious adverse events were higher in the surgical group (2%) though the PNF group also had a serious adverse event (flexor tendon rupture).

In addition to the study by Räisänen et al. there are 2 other RCTs comparing PNF with surgical fasciectomy, both with published 5-year follow-up results [97, 136] (Table 1). Although these 2 studies differ in methodology as van Rijssen et al. performed standard PNF while Selles et al. performed extensive PNF combined with lipofilling, both showed higher recurrences after PNF than after surgical fasciectomy [102, 137].

Table 1. Recurrence rates in RCTs comparing percutaneous needle fasciotomy with surgical fasciectomy

Author	Year	Longest follow-up	Treated joint	n	Primary outcome	Definition recurrence	Recurrences %
Van Rijssen et al. [97]	2012	5 years	MCP & PIP	93	Recurrence	TPED Increase ≥30° from 6-week follow-up	PNF 85% Surgical fasciectomy 21%
Selles et al. [136]	2018	5 years	MCP & PIP	52	Recurrence	Secondary treatment or TED Increase ≥20° from 3-week follow-up	PNF 74% Surgical fasciectomy 39%

MCP, Metacarpophalangeal; PIP, Proximal interphalangeal; PNF, Percutaneous needle fasciotomy; TED, Total extension deficit; TPED, Total passive extension deficit.

While there are few RCTs comparing PNF with surgical fasciectomy, 5 RCTs comparing PNF with collagenase have been published (Table 2) [52, 105, 138-140], in addition to the study by Räisänen et al. comparing all treatment methods. Despite several studies with follow-up time ranging between 1 and 5 years (2 of these RCTs with several follow-up times published) only 1 of these have a published follow-up longer than 3 years [52, 105, 138-140]. In short, outcomes in these 5 studies are similar between collagenase and PNF but with a higher incidence of complications after collagenase [52, 105, 138-140]. However, the definition of complications differs between the studies, and the well-known side effects of collagenase treatment described by Hurst et al. [49] are often reported as complications.

Table 2. Recurrence rates in RCTs comparing percutaneous needle fasciotomy with collagenase

Author	Year	Longest follow-up	Treated joint	n	Primary outcome	Definition recurrence	Recurrences %
Skov et al. [52]	2017	2 years	PIP	42	Contracture reduction >50% compared to baseline	PIP PED >20°	PNF 68% CCH 83%
Scherman et al. [138]	2018	3 years	MCP	76	Recurrence	TPED Increase ≥30° from 3-month follow-up	PNF 43% CCH 33%
Abe et al. [139]	2020	3 years	MCP & PIP	70		TED increase ≥20° from 30 day follow up	PNF: 29% MCP, 38% Stage 1 PIP, 67% stage 2 PIP CCH: 26% MCP, 44% Stage 1 PIP, 67% stage 2 PIP
Byström et al. [105]	2022	5 years	MCP	143	Complete contracture (PED<5°)	TED >20°	PNF 45% CCH 56%
Jørgensen et al. [140]	2023	3 years	MCP	68	Recurrence	PED increase ≥20° or secondary treatment	PNF 47% CCH 19%

CCH, Collagenase Clostridium Histolyticum; MCP, Metacarpophalangeal; PED, Passive extension deficit; PIP, Proximal interphalangeal; PNF, Percutaneous needle fasciotomy; TED, Total extension deficit; TPED, Total passive extension deficit.

In the comparison of collagenase vs surgical fasciectomy, Räisänen et al. found as previously described, that treatment success was better maintained after surgical fasciectomy than after collagenase [135]. This is also consistent with a recent systematic review that included 11 studies comparing collagenase with surgical fasciectomy, showing higher recurrence but fewer serious adverse events after collagenase than after surgical fasciectomy [141]. Furthermore, a non-inferiority RCT was recently published comparing collagenase with surgical fasciectomy using the 1-year patient evaluation measure (PEM) score (a PROM that measures hand function) as the primary outcome. In this study collagenase was not noninferior to surgical fasciectomy regarding the primary outcome while complications were more common in the surgical group [142].

There is also a published RCT comparing collagenase with surgical fasciectomy with a 1-year follow-up indicating similar outcomes for the 2 treatments [143]. However, since only 21 of the calculated sample size of 128 patients were recruited, this RCT is underpowered (as the authors clearly state) and its value is questionable [143]. According to the authors of the study the failure to recruit patients was partly due to too strict inclusion criteria, patient preference for minimal invasive treatment and collagenase discontinuation in Canada.

Finally, no RCTs comparing treatment modalities for recurrent disease have been published, but an RCT comparing 1-year outcomes for collagenase with surgical fasciectomy for recurrent disease will be presented more thoroughly later in this thesis.

Chapter 2: Aims

2.1: General aims

The main aim of this thesis was to improve knowledge about Dupuytren disease, specifically regarding treatment effect durability, recurrence and patient-reported outcomes.

2.2: Specific aims

I. To assess the long-term (5 years) outcomes of pharmacological treatment with collagenase injection for Dupuytren disease and investigate risk factors that can predict recurrence.

II. To compare the prevalence of joint contractures in fingers treated with collagenase injection and fingers treated with surgical fasciectomy 5 years after treatment for Dupuytren disease.

III. To assess methodological quality and risk of bias in published randomized controlled trials comparing collagenase injection with percutaneous needle fasciotomy.

IV. To compare the short-term results regarding joint contracture, adverse events and patient-reported outcomes between surgical fasciectomy and collagenase injections when treating recurrent Dupuytren disease.

V. To investigate the responsiveness of the COPM and the QuickDASH in patients treated with collagenase injection for Dupuytren disease.

VI. To develop a novel patient-reported outcome measure, specific for Dupuytren disease.

Chapter 3: Patients and methods

This thesis is based on 6 papers (Figure 8) that investigate the field of Dupuytren disease. This thesis will continue with a brief description of the different study designs and setting for the included papers.

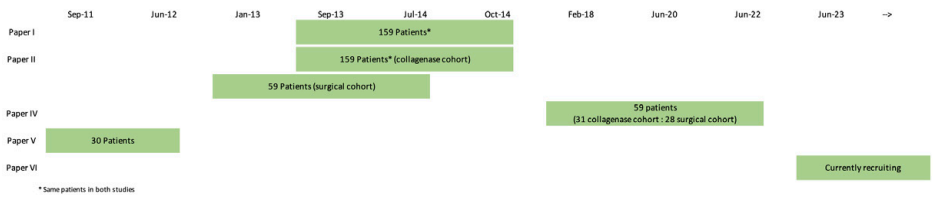


Figure 8. Study timelines

3.1: Study designs and settings

Papers I & V are single-center prospective cohort studies while *paper II* is a comparative cohort study. *Paper III* is a systematic review that investigates the methodological quality and risk of bias in published RCTs that compare collagenase with PNF. *Paper IV* is the 1-year outcomes of an ongoing RCT comparing collagenase injection with surgical fasciectomy for recurrent Dupuytren disease. Finally, *Paper VI* is the study protocol describing the ongoing study that aims to develop a novel Dupuytren-specific PROM using IRT methodology.

Papers I, II, IV & V all use data from the orthopedic department at Hässleholm-Kristianstad hospitals in northeast Skåne, a southern Swedish orthopedic university department serving approximately 300 000 inhabitants. *Paper VI* is a multicenter study including data from the same center as well as from the Hand surgical department at Skåne University hospital, Malmö, Sweden and Fife Hand Clinic at Victoria Hospital, Kirkcaldy, Scotland. *Paper III* is a systematic review and did not include any recruitment of patients.

3.2: Interventions

Collagenase injection

The collagenase treatments in *papers I, II, IV, and V* were all performed by a single hand surgeon according to a modified technique that differs in some aspects from the method first described by Hurst et al [49]. These are (1) use of local anesthesia (LA) before collagenase injection and finger manipulation [113], (2) use of a higher dose of collagenase (1 vial corresponding to approximately 0.8 mg) and, when needed for multiple fingers, use of 2 vials [144], and (3) The distribution of collagenase over multiple (3-4) injection sites in the cord, between the palmar crease and the PIP joint [144].

Collagenase injection and finger manipulation were performed in 2 separate outpatient visits with an interval of 1-2 days. Before injection joint ROM was measured by an occupational hand therapist. Patients then received LA followed by collagenase injection according to the modified technique as described above. After injection all patients received a soft dressing by an assisting nurse and verbal instructions regarding edema prophylaxis and to avoid heavy use of the hand. When returning to the outpatient clinic after 1-2 days finger manipulation was performed after administration of LA with the intention of achieving best possible extension regardless of potential skin tears [108].

An occupational hand therapist equipped patients with a customized static splint (to keep fingers in best possible extension) and gave finger exercise and edema prophylaxis instructions immediately after extension. One week following finger manipulation patients had a follow-up visit with an occupational hand therapist during which the splint was adjusted. The advice was to use the splint at night for 8 weeks. Further visits to the occupational hand therapist were scheduled if needed. If skin tears occurred these were treated conservatively with dressings until healed. For patients with residual contracture, additional injections were scheduled after discussion between the surgeon and the patient.

Surgical fasciectomy

All surgical fasciectomies in *papers II and IV* were performed by experienced surgeons. In paper II the procedures were performed by 8 different surgeons (3 hand surgeons, 5 orthopedic surgeons) and in *paper IV* the procedures were performed by 2 surgeons (1 orthopedic surgeon and 1 hand surgeon [not the same hand surgeon that performed collagenase injections]). In both studies, the surgeons were allowed to select the type of incision according to their preference followed by a standard surgical fasciectomy procedure removing all possible diseased fascia. Capsulotomy of the PIP joint was done when deemed necessary by the surgeon. All patients

received soft dressings which were changed at an outpatient visit to a nurse after 5-7 days. All patients met an occupational hand therapist (in *paper* IV the occupational hand therapist was not involved in the study) for instructions and received a splint positioning the treated finger in best achievable extension to be used for 3 months after surgery. Sutures were removed 2 weeks after surgery.

3.3: Follow-up procedures

Clinical examination

Extension deficit was used as an outcome measure in *papers I, II, IV* and *V.* All measurements were performed as recommended by the Swedish National manual for measuring motion and strength in the elbow, forearm and hand [145]. The patient was sitting with the elbow flexed resting on a table with the forearm and wrist in neutral position. MCP and PIP joints were measured separately on the dorsal side of the finger using a hand-held metal goniometer. For AED the examiner asked the patient to extend the fingers as much as possible and then measured AED for each respective joint without applying any additional pressure. When measuring PED, the same procedure was repeated but the examiner applied a light pressure (without using excessive force) to reach the maximal extension possible. PED was measured separately for the MCP and PIP joints, and to reduce the influence of dynamism, PIP measurements were made with MCP joints in full extension [146].

For papers *I, II and V* all baseline measurements were routinely performed by an occupational hand therapist that measured AED and PED for the MCP and PIP joints of the 3rd, 4th and 5th finger as part of the collagenase treatment protocol. The follow-up measurements were performed in the same manner by either an orthopedic resident or an occupational hand therapist (*papers I & II)* or by occupational hand therapist (*paper V*).

Since *paper IV* was an RCT with a published pre-trial study protocol, all measurements were performed in accordance with this protocol. Thus, all baseline as well as follow-up measurements were performed by 2 occupational hand therapists otherwise not involved in patient care and who were blinded for which treatment patients had been randomized to and patients used gloves with open fingertips on their treated hand to hide potential scarring. For all patients, grip strength using a dynamometer was also measured and sensation was evaluated using Semmes-Weinstein monofilaments.

Patient-reported outcome measures

PROMs were used as outcome measures in all the clinical studies included in this thesis (*papers I, II, IV, V & VI*) as specified below.

Paper I: The examiner asked the patient to verbally rate their treatment satisfaction on a 5-point scale (1 = very satisfied, 2 = satisfied, 3 = rather satisfied, 4 = neutral, 5 = dissatisfied). The patients completed the 11-item QuickDASH questionnaire (score range 0 = best – 100 = worst) at the 5-year follow-up.

Paper II: the patients completed the 11-item QuickDASH questionnaire at the 5-year follow-up.

Paper IV: Several PROMS were used in *Paper IV,* all filled out at baseline, 3, 6 and 12 weeks as well as 1 year after treatment. PROMs included the 11-item QuickDASH, the EQ5D (score range -0.594 = worst – 1.0 = best). The palmar pain scale, (score range 0 = best – 100 = worst). PROMs were also used to assess cold intolerance. For the first 11 consecutive patients, cold intolerance was measured with the 6-item cold intolerance symptom severity scale (CISSS) (score range 4 = best –100 = worst). However, because of substantial missing and inconsistent responses, the CISSS was abandoned. For remaining patients, a 2-item scale (similar to the palmar pain scale) inquiring about the severity of cold intolerance and its effect on daily activities was used (score range 0 = best – 100 = worst). Patients also rated their pain and treatment satisfaction on visual analogue scales (VAS) (score range 0 = best – 100 = worst).

Paper V: At baseline and at 5 weeks after treatment the patients answered the 11-item QuickDASH followed by an interview according to the COPM.

Paper VI: The first 300 included patients will be asked to fill out an extensive questionnaire developed by an expert group consisting of orthopedic surgeons, hand surgeons and occupational hand therapists, all with experience of treating patients with Dupuytren disease, using items from previously existing PROMs as well as feedback from patients. The final questionnaire begins with 2 questions regarding hand dominance, and which hand the patient is seeking healthcare for. These are followed by 85 items inquiring about activity limitations, symptoms, and other issues, concluding with 1 free-response question allowing patients to list 3 additional activities and rate their ability in performing them. The responses provided by the patients will then be analyzed to identify the best performing items and create a new PROM. The new Dupuytren-specific PROM will be administered to a validation sample of 300 patients.

Adverse events

For *Papers I & II* data regarding adverse events after collagenase injection such as skin tears, infection, complex regional pain syndrome were routinely documented

during treatment and at follow-up visits. For the surgical fasciectomy cohort in *paper II* adverse events were not routinely documented, but available information was extracted from the patients' medical record. For *paper IV* patients were routinely screened for adverse events at 1 and 12 weeks after treatment according to a pre-established protocol, and if adverse events were present at 12 weeks patients were also screened at 1 year. For *Paper V* adverse events were not routinely documented and since no treatments were performed in *Papers III & VI* adverse events were not recorded.

3.4: Paper-specific methods and statistics

In the following section the specific methods as well as the statistics of each of the different papers will be described separately. In general, SPSS (v25), STATA (v16) and R (v4.2.2) were used for the statistical analyses. A 2-sided p-value <0.05 was used to indicate statistical significance in papers I, II, IV, V & VI. Data is presented as either means with standard deviations (SD) or as percentages in all included papers. In all papers hyperextension was recorded as 0° extension deficit.

Paper I

Methods

Paper I was a single-center prospective cohort study. Patients with a joint contracture of ≥20° in either the MCP or PIP joint or both were eligible for treatment. All patients treated at the center for Dupuytren disease with collagenase injection, in ≥1 of the 3 ulnar fingers between September 2013-October 2014 qualified for inclusion. For all treated patients, ROM was routinely measured and documented by an occupational hand therapist (independently from the treating surgeon) before and approximately 6 weeks after treatment.

Patients treated with subsequent surgical fasciectomy during the follow-up were considered to have had recurrence and met the end criteria. The remaining patients including those that had received additional collagenase injections (PNF was not performed at the center during the study period) were invited per mail to attend 5-year follow up including measurement of joint contracture by either an orthopedic resident or an occupational hand therapist. The primary outcome was recurrence, defined as AED ≥20° in a treated joint or subsequent surgical fasciectomy or collagenase injection. Secondary outcomes included PROMs (QuickDASH and treatment satisfaction). Risk factors for recurrence were also analyzed.

Statistics

Mean AED with SD was calculated at baseline and 6 weeks as well as at 5 years after treatment with collagenase injection. Difference in mean AED between baseline and 6 weeks and between 6 weeks and 5 years was calculated with 95% CI and analyzed with the paired t-test. Recurrence was defined as worsening of AED ≥20° between 6 weeks and 5 years in a treated joint and this was used as the primary outcome. Complete correction is traditionally calculated using PED, but AED was used in this study. The proportion of joints with a baseline joint contracture ≥20° with AED ≤ 5° was calculated. To determine risk factors for recurrence, a mixed-effect regression model was used, and odds ratios (OR) and CI were calculated for both MCP and PIP joints. Two models were used: one that considered repeat injections as recurrence and another that did not consider repeat injections as recurrence. The covariates in both models were age, sex, baseline contracture, small-finger treatment, previous treatment with surgery or injection, diabetes, and smoking status. Mean and SD QuickDASH scores were calculated at 5 years. The proportions of patients reporting that they were dissatisfied, neutral, rather satisfied, satisfied or very satisfied on the patient-reported satisfaction scale were calculated (all patients treated with subsequent surgical fasciectomy during follow-up time were considered dissatisfied).

Paper II

Method

Paper II was conducted as a single center comparative cohort study comprising of 2 cohorts, the same prospective collagenase cohort as in *paper I* and a retrospective surgical cohort treated with surgical fasciectomy. The primary outcome was the percentage of treated joints with ≥20° of joint contracture after 5 years. The secondary outcome was the total (MCP+PIP) active extension deficit (TAED) in a treated finger. As in *paper I* the indication for treatment was ≥20° joint contracture in either MCP or PIP joints. Inclusion criteria were patients treated for Dupuytren disease ≥1 of the 3 ulnar fingers with either collagenase between September 2013 and October 2014, or surgical fasciectomy between January 2013 and July 2014. As previously mentioned in *paper I* ROM for collagenase-treated patients was routinely measured before and after treatment, while baseline joint contractures for the surgical fasciectomy cohort were extracted from medical records. As in *paper I* patients who had received secondary treatment with surgical fasciectomy during the follow-up period were considered to have had at least 20° of joint contracture and they were not invited to attend 5-year follow-up. The remaining patients were invited per mail and, when necessary, by phone to attend 5-year follow-up including measurements of joint contracture.

Statistics

Mean AED and SD were calculated for both cohorts at baseline and at 5 years. The baseline to 5-year differences with 95% CI were then calculated. The proportion of treated joints with AED ≥20° at 5 years was defined as the primary outcome, and TAED at 5 years as secondary outcome. Due to the lack of early postoperative joint contracture data for the fasciectomy cohort, recurrence could not be calculated. Instead, the 5-year contractures were defined as current contractures. To compare the 2 cohorts regarding change in joint contracture over time, linear mixed models were used. One unadjusted model and one model adjusting for age, sex, small-finger treatment, previous injection, and previous fasciectomy were performed. Two similar models were then constructed (1 unadjusted model and 1 model adjusting for the same variables as the previous model) using joint contractures before subsequent treatment as 5-year values. As in paper I complete correction was defined as AED ≤5° in a treated joint with a pre-treatment contracture of ≥20°.

Paper III

Method

Paper III was conducted as a systematic review assessing the methodological quality and the risk of bias in published RCTs comparing collagenase injections with PNF for Dupuytren disease. A literature search of PubMed and Cochrane databases was conducted, and 2 researchers screened all studies published before May 2023 for inclusion, first by title/abstract and then by full text. Prospective RCTs comparing collagenase with PNF were eligible for inclusion. Follow-up studies of the same cohorts as in previously published studies were excluded. The included studies were then assessed for methodological quality and risk of bias independently by 1 of the researchers who had performed the initial screening and another researcher who was blinded to the authors of the study, title, year of publication, origin of the study, journal and any other data that may identify the study. For methodological quality the researchers used the Jadad score (score range 0 [worst] to 5 [best]) as modified by Gummesson et al. [147] which assess the method of randomization, blinding, and dropouts/withdrawals. Due to the large number of non-described exclusions before randomization these exclusions were considered as dropouts/withdrawals. For risk of bias, we used the revised tool to assess risk of bias in randomized trials (RoB2) [148] which assess 5 domains (randomization, blinding, availability of data, outcome analysis and adherence to a prespecified protocol). RoB is then graded as either low risk of bias, some concern or high risk of bias according to an algorithm. The goal was to reach consensus and when the researchers were not in agreement, they continued discussions to try to reach consensus before a third researcher was consulted. RCT registries were searched for pre-trial study protocols and in cases when those could not be found the ethics review boards or the authors were

contacted to be able to compare these protocols with the published articles for potential discrepancies.

Statistics

No statistical analyses were performed in *paper III.*

Paper IV

Method

Paper IV Is the 1-year follow-up of an ongoing single-center randomized controlled trial comparing collagenase with surgical fasciectomy for recurrent Dupuytren disease. The primary outcome was change in TAED in a treated finger from baseline to 12 weeks and co-primary outcome (which will be analyzed in a future publication when 2-year outcomes are available) was the proportion of joints with recurrence between 12 weeks and 2 years. Secondary outcome measures included change in total active motion (sum of total range of motion in MCP, PIP and distal interphalangeal joints), change in TAED between baseline and 1 year, change in TPED in a treated finger from baseline to 12 weeks and 1 year, change in PROMs, as well as adverse events. All patients with recurrent Dupuytren disease, referred to the study center were screened for inclusion by either a hand surgeon or orthopedic surgeon. The inclusion criteria were patients ≥18 years of age, recurrent Dupuytren disease after previous treatment with collagenase or surgical fasciectomy, or (after an amendment of the study protocol) PNF, no Dupuytren treatment in the affected hand during the last 12 months, and a palpable cord causing a contracture with a PED of 30° in either MCP, PIP or both joints in ≥1 of the 3 ulnar fingers. The exclusion criteria included: any medical comorbidities preventing any of the trial treatments, severe osteoarthritis of the joints of the affected finger, previous trauma or non-Dupuytren surgery to the affected finger, clinical signs of previous neurovascular injury or established complications of previous treatment such as infection, neurovascular injury or complex regional pain syndrome, >2 previous treatments with surgical fasciectomy or collagenase, previous treatment with both methods, and if the treating surgeon considered further surgical fasciectomy is associated with a very high complication risk.

Patients who fulfilled all inclusion criteria and none of the exclusion criteria and accepted inclusion were randomized by a computer-generated sequence in blocks of 4 or 6 to either surgical fasciectomy or collagenase injection (1:1 ratio). The randomization was stratified according to previous treatment (collagenase/PNF or surgery) as well as affected finger (small finger treated, yes/no). Baseline clinical examination including testing of grip and pinch strength and testing of sensitivity were performed as well as ROM measurements as previously described. Baseline data including occupation, bilateral disease, heredity, smoking or diabetes were

recorded and PROMs were collected from all included patients. The patients were put on waiting list for either collagenase injection or surgical fasciectomy to be carried out within the coming months. After treatment, follow-ups were performed according to a pre-established schedule:

- 1 week (adverse event screening)
- 3 weeks (PROMs)
- 6 weeks (PROMs)
- 12 weeks (PROMS, clinical examination and adverse event screening)
- 52 weeks (PROMs and clinical examination and screening for adverse events if any were present at 12 weeks.

Statistics

The primary outcome was the change in TAED in a treated finger from baseline to 12 weeks and the co-primary outcome was the proportion of joints with recurrence between 12 weeks and 2 years.

The sample size was calculated based on the assumption that a difference of 20° in TAED is clinically relevant. Thus, to be able to show a difference of ≥20° between the groups at 12 weeks and using SD of 25, alpha level of 0.05 and a statistical power of 80%, 25 patients per group would be required.

Mean and SD AED and PED were calculated for each joint at baseline, 12 weeks, and 1 year and summarized to TAED and TPED. For the primary outcome a mixed effects linear model was used (to account for some patients providing data for multiple fingers) to analyze the change between baseline and 12 weeks in mean TAED and adjusting for age, sex, previous treatment (minimal-invasive or surgical fasciectomy), number of previous treatments, treated finger (small finger treated vs not treated) and TAED before treatment. Adjusting for the same variables a similar model was used to analyze change in TAED between 12 weeks to 1 year and change in TPED between baseline to 12 weeks and between 12 weeks to 1 year. Since all 5 patients previously treated with PNF were randomized to the collagenase the same analyses for TAED and TPED were performed after excluding these patients. Linear regression models were then used to analyze change in QuickDASH, pain score, cold sensitivity adjusting for baseline PROM score, age, sex, previous treatment, and number of treated fingers. The change in EQ5D score was compared between the groups using the independent samples t-test. For VAS satisfaction the mean and SD values at each respective follow-up are presented.

Paper V

Method

Paper V was a prospective cohort study investigating the short-term (5 weeks) outcomes after collagenase injection with the COPM. Patients receiving treatment with collagenase for Dupuytren disease between September 2011 and June 2012 were eligible for inclusion. Patients accepting inclusion were interviewed according to the COPM, listing and rating their performance and satisfaction for up to 5 different activities and completed the QuickDASH at baseline and 5 weeks after treatment. As in previous papers, all patients also had their joint contractures measured before and after treatment according to the standard routine for collagenase treatments at the time of the study.

Statistics

The difference in COPM score for both performance and satisfaction was calculated by subtracting the baseline score from the 5-week follow-up score. Clinically important change in score has previously been defined as a change of ≥2, but in later research ≥3 has been advocated [149, 150]. Calculations for improved score based on ≥2 points and ≥3 points were performed. Median scores and quartiles for the COPM and QuickDASH at baseline and 5 weeks were calculated, and the change was analyzed with the Wilcoxon test. The mean TAED at baseline and 5 weeks was calculated and the correlations between TAED and COPM and QuickDASH scores were analyzed using the Spearman correlation coefficient. Cohen's d was used as measure of responsiveness. Cohen's d values of 0.2 indicate small, 0.5 moderate and ≥0.8 indicates a large clinical change [151]. TAED of the treated finger was defined as the criterion for comparison.

Paper VI

Method

Paper VI is the study protocol for the development of a new Dupuytren-specific patient-reported outcome measure. The study is divided into 3 phases.

In the **first phase** of the study (completed), an expert group consisting of orthopedic surgeons, hand surgeons and occupational hand therapists, all experienced in treating Dupuytren disease, constructed a large questionnaire from pre-existing PROMs and patient feedback.

In the **second phase** of the study, all patients with Dupuytren disease (regardless of disease severity and any possible previous treatments) referred to the study centers will be screened according to pre-established inclusion criteria by either a hand surgeon or an orthopedic surgeon.

Inclusion criteria

- Dupuytren disease diagnosed by either an orthopedic surgeon or a hand surgeon
- Age ≥18 years
- Patient able to independently understand and consent to participation

Exclusion criteria

- Cognitive impairment
- Inability to independently complete the questionnaire
- Patient unwilling to participate

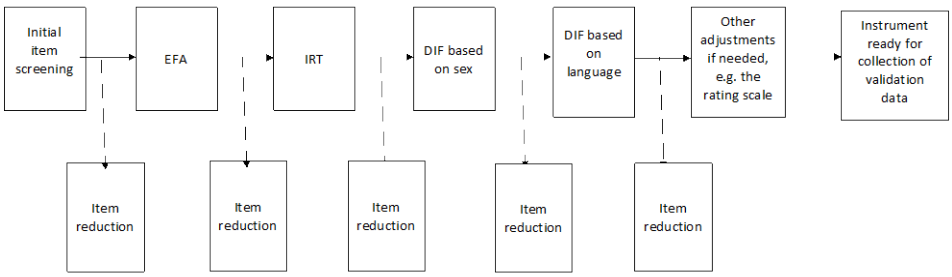
After inclusion, baseline data regarding comorbidities, heredity, profession, previous treatment, affected digit and hand, signs of bilateral disease as well as measurements of joint contracture will be collected. Included patients will also complete the questionnaire developed in the first phase of the study in the weeks before or after their doctors appointment. When the preestablished sample size of 300 patients has been completed, IRT methodology will be used to analyze responses and to create a new PROM.

In the **third phase** of the study, the newly developed PROM will be administered to an additional 300 patients both prior to and after treatment. These responses will then be analyzed in a similar manner using IRT to validate the PROM while additional analyses will also be performed to establish responsiveness and to investigate if any items are more responsive for certain groups of patients or joints.

Statistics

As there is no defined minimal sample size when developing PROMs, we estimated the sample size (to be able to meet the requirements for the planned statistical analyses) to 300 patients [152]. When the sample size has been met, the mean and SD values for PED for each joint and for TPED will be calculated. Demographic characteristics will be described and the proportion of patients with bilateral disease, diabetes, family history of Dupuytren disease, and current smoking will be calculated. Patients' responses to the questionnaire will be analyzed as described in Figure 9. Analysis will begin with initial item screening to exclude items that are too rarely identified as difficult to perform to be included in the final PROM. Exploratory factor analysis (EFA) will then be performed using Mplus [153]. This will be followed by IRT analysis for the remaining items and as part of the IRT analysis the items will be examined with regard to Differential Item Functioning (DIF) (when patients from different groups such as different sex but with the same

level of the latent trait such as functioning or symptoms have different expected scores on an item) for both sex and language. Finally other adjustments such as adjustments of the rating scale will be performed if needed before the new PROM is finalized. The new PROM will then be distributed to an additional 300 patients for field testing, and their responses will be analyzed in a similar manner as for the development phase to validate the new PROM.



EFA, Exploratory factor analysis; IRT, Item response theory; DIF, differential item functioning

Figure 9. Scheme of the planned statistical analyses for the development of the new PROM

3.5: Ethics, funding and conflicts of interest

Ethical considerations were made before each of the studies included in this thesis and all studies were performed according to the Helsinki declaration as revised in 2000. *Papers I, II, IV, V & VI* were all ethically reviewed by an ethics review board before initiation, while *Paper III* as a systematic review did not require authorization by the ethics review board. *Paper I* (DNR 2013/656), *Paper II* (DNR 2013/656 & 2018/975), *Paper IV* (DNR 2017/623 & 2020-05342), *Paper V* (DNR 2013/656), *Paper VI* (DNR 2023-01725-01 & 2023-05885-02). All patients in *papers I, II, IV, V & VI* received verbal and written information before they consented to inclusion and all included patients could withdraw their consent at any given time without specifying the reason.

The authors received support from region Skåne for the *papers I, II, IV, V and VI*, while *paper III* received no funding. The author of the thesis received grants from Guldbyxan foundation to support the writing of the dissertation. The author of the thesis has no conflict of interest to report. No pharmaceutical or medical technology company supported any of the research included in this dissertation.

Chapter 4: Results

In the following section results from the included papers will be presented separately. Baseline patient characteristics for the different papers are presented in Table 3.

Table 3: Patient characteristics at baseline.

	Paper I	Paper II Collagenase : Surgery	Paper IV Collagenase : Surgery	Paper V
No. of patients	126	112 : 46	31 : 28	30
Age, mean (SD) y	69 (8)	69 (8) : 65 (10)	72 (9) : 71 (6)	67* (55-79)
Sex, n (%)				
Men	112 (89)	100 (89) : 38 (83)	28 (90) : 25 (89)	21 (70)
Women	14 (11)	12 (11) : 8 (17)	3 (10) : 3 (11)	9 (30)
Smokers, n (%)	17 (14)	17 (15) : 11 (24)	0 (0) : 2 (7)	NA
Diabetes, n (%)	12 (10)	11 (10) : 11 (24)	2 (7) : 4 (15)	NA
Treated hand, n (%)				
Right	83 (57)	74 (58) : 25 (51)	15 (48) : 16 (55)	70% dominant hand
Left	62 (43)	54 (42) : 24 (49)	16 (52) : 13 (45)	
Treated finger, n (%)				
Middle	30 (15)	30 (17) : 4 (6)	4 (10) : 3 (9)	
Ring	74 (37)	66 (37) : 26 (41)	16 (41) : 11 (33)	12 (39)
Small	95 (48	84 (47) : 33 (52)	19 (49) : 19 (58)	19 (61)
Previous treatment, n (%)				NA
Surgery	16 (8)	16 (9) : 10 (16)	6 (19) : 6 (21)	
Collagenase/PNF	8 (4)	7 (4) : 9 (14)	25 (81) : 23 (79)	
AED, mean (SD) degrees				
TAED	72 (36)	72 (37) : 75 (27)	65 (26) : 69 (25)	85 (60, 115)#
MCP	42 (24)	43 (24) : 36 (25)	NA	NA
PIP	31 (29)	29 (29) : 45 (29)	NA	NA

*Median (range)
#Median (IQR)
AED, active extension deficit; MCP, metacarpophalangeal; PIP, proximal interphalangeal; PNF, percutaneous needle fasciotomy; TAED, total active extension deficit.

4.1: Paper I

During the study period, 159 patients were treated with collagenase injection at the study center. At 5 years, 2 patients could not be reached, 18 were deceased and an additional 13 had undergone surgical fasciectomy during the follow-up period, thus considered to have reached the endpoint and were not invited to 5-year examination. All remaining 126 patients attended 5-year follow-up either per telephone (n=12) or physical examination (n=114). Mean time to follow-up was 65 months (SD 9). Among patients attending follow-up mean age was 69 (SD 8) years and 89% were men. Contractures of the small finger constituted 48% of the treatments. Skin tears occurred in 35% of treatments, and 1 patient had a complex regional pain syndrome that healed with hand therapy.

Mean TAED was 72° (SD 36) at baseline, 20° (SD 21) at 6 weeks and 31° (SD 32) at 5 years. The mean difference in TAED was 53° (95% CI 49° to 56°) between baseline and 6 weeks (improvement) and -11 (95% -15° to -8°) between 6 weeks and 5 years (worsening). Recurrence defined as either worsening of contracture ≥20° in a treated joint or repeat treatment (surgical fasciectomy or collagenase injection) was found in 17% of MCP joints and 25% of PIP joints.

No statistically significant risk factors could be identified for MCP joint contracture recurrence. For PIP joints, a greater baseline contracture (OR 1.04, 95% CI 1.02-1.06), and treatment of the small finger (OR 4.6, 95% CI 1.5-14.3) were identified as independent risk factors for recurrence.

The mean QuickDASH score was 10 (SD 12) at 5 years and 49% of patients rated that they were very satisfied with the treatment, 18% were satisfied, 10% were rather satisfied, 8% were neutral, and 25% were dissatisfied (including the patients that had undergone subsequent surgery).

4.2: Paper II

159 patients in the collagenase cohort and 59 patients in the surgical cohort were treated during the study period. The surgical patients were treated by 8 different surgeons while all patients in the collagenase cohort were treated by 1 hand surgeon. At 5 years, 13 patients in the collagenase cohort were deceased, and 13 had received surgical fasciectomy for recurrence while an additional 21 declined participation or could not be contacted. For the surgical cohort, no patients were deceased but 8 had received subsequent treatment (fasciectomy or collagenase injection) and an additional 5 patients declined participation or could not be contacted. Thus 112 patients in the collagenase cohort (89% men, mean age 69 [SD 8] years) and 46 patients in the surgical cohort (83% men, mean age 65 [SD 10] years) attended 5-

year examination. Baseline mean TAED in the collagenase group was 72° (SD 37) and in the surgical group 75° (SD 27). Adverse events occurred in both groups. In the collagenase cohort, skin tears occurred in 35% of treatments (all healed with wound care) and 1 patient had a mild complex regional pain syndrome that resolved with hand therapy. In the surgical cohort, data about adverse events was missing for 13%, 5% had postoperative wound infections that healed with antibiotics and for the remaining 81% no adverse events were documented in the medical records. At 5 years, mean TAED was 27° (SD 30) and 35° (SD 34) for the collagenase and surgical groups, respectively. In the collagenase cohort, a current contracture ≥20° was found in 45 MCP joints (25%) and 60 PIP joints (33%). In the surgical cohort a current contracture was found in 12 MCP (19%) and 30 PIP joints (48%). The mean QuickDASH scores in both cohorts were similar. In the linear mixed model, no statistically significant difference between the 2 cohorts could be found regarding change in total active extension deficit over time.

4.3: Paper III

The initial search resulted in 105 studies, and after removal of 94 studies by automation tools (not RCT studies) 11 remained for screening. After title and abstract screening of these 11 studies, 6 were excluded for the following reasons: 1 not a comparison between collagenase and PNF, 1 study protocol, 3 follow-up studies of previously published studies that were potentially eligible for inclusion in this systematic review, and 1 discussion article of previously published study. After full text screening of the remaining 5 RCTs none were excluded, thus 5 RCTs [50-52, 139, 140] (2 from Denmark, 2 from Sweden and 1 from Japan) comprising a total of 204 patients treated with collagenase and 209 patients treated with PNF were included and analyzed for methodological quality using the modified Jadad score and for risk of bias using the RoB 2 tool.

All 5 RCTs were found to have a high risk of bias (Figure 10) and for methodological quality, the modified Jadad score ranged from 1 to 2 points. While all studies were described as randomized, the randomization method was judged as appropriate in 2 studies, inappropriate in 2 and not described in 1. Furthermore, while 2 studies were described as blinded only 1 of these described an appropriate method of blinding while the other did not describe the method. Finally only 1 of the 5 studies described withdrawals/dropouts but this study fails to present data regarding the number of screened patients, while the remaining 4 studies describes the number of screened patients but without presenting the reasons for exclusions.

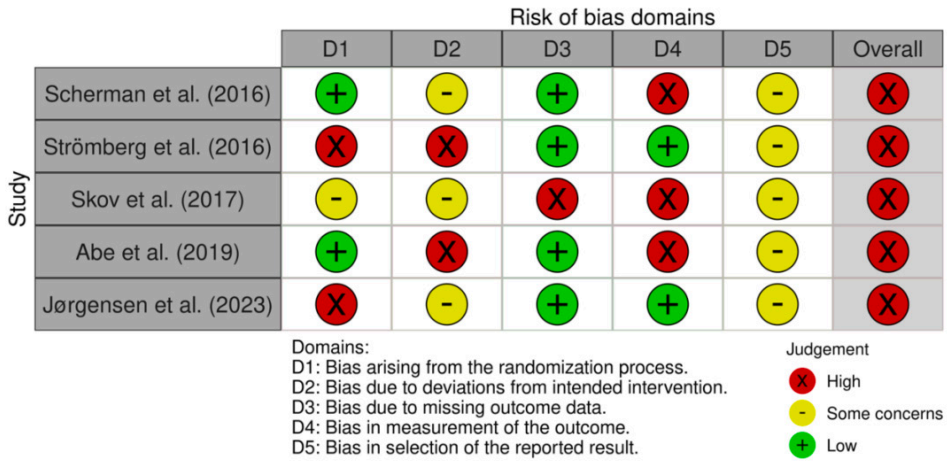


Figure 10. Risk of Bias of the included 5 RCTs [50-52, 139, 140] (reprinted from EFORT Open Reviews [154])

Pre-trial study protocols could be retrieved for 2 of the 5 studies and discrepancies with the published articles were found in both. 1 protocol stated that contracture affecting MCP or PIP joint were eligible for inclusion if the contracture was "large enough" but in the final article this had been changed to contracture "primarily affecting the MCP joint". The other protocol also stated that contractures affecting the MCP or PIP joint were eligible for inclusion but in the final article inclusion criteria is stated as patients with isolated MCP joint contracture unless the patient "accepts that any PIP contracture would be left untreated". Trial registration in RCT registries could be found for only 2 of the 5 studies, 1 of which did not differ from the final published article, while but the other was brief with no clearly stated inclusion criteria and created after the initial submission of the manuscript.

4.4: Paper IV

60 patients (61 hands, 74 fingers) were randomized (31 patients to collagenase and 29 to surgical fasciectomy). 1 patient (1 finger) randomized to surgery declined treatment and was excluded. Thus 59 patients (60 hands, 72 fingers) received their allocated treatment: 31 patients (31 hands, 39 fingers) in the collagenase group and 28 patients (29 hands, 33 fingers) in the surgical fasciectomy group. 1 patient in the surgery group withdrew from the study 6 weeks after surgery, and 1 patient attended the 12-week examination on a later occasion but completed PROMs as scheduled, leaving 58 patients (59 hands, 71 fingers) completing the 12-week follow-up. All

patients who completed the 12-week follow-up also completed 1-year PROMs but 2 patients (1 treated finger per patient) both in the surgical group, missed the 1-year clinical examination, 1 due to the covid pandemic and 1 due to severe medical illness.

For the primary outcome (change in TAED from baseline to 12 weeks), the linear mixed-effects analysis showed no statistically significant difference between the 2 groups. Furthermore, no statistically significant differences were found between the 2 groups in TAED or TPED at baseline, 12 weeks or 1 year and no statistically significant differences were found between the 2 groups regarding TAED change from baseline to 1 year or regarding TPED change from baseline to 12 weeks, or from baseline to 1 year. There was a significant difference (linear mixed-effects analysis) regarding change in QuickDASH score from baseline to 3 weeks and from baseline to 6 weeks, favoring collagenase. For all other PROMs, no statistically significant differences were found between the 2 groups.

None of the included patients underwent any subsequent treatments during the 12-month follow-up. Adverse events occurred in both cohorts. In the surgical cohort serious adverse events were recorded for 3 patients at the day of treatment (2 vascular injuries and 1 digital nerve laceration). The most common adverse event was in the collagenase group full thickness skin rupture (n=9) and in the fasciectomy group was disturbed sensation (n=18). At the 1-year follow-up, 9 patients in the fasciectomy group and 2 patients in the collagenase group still had disturbed sensation. There were no cases of tendon injury, deep infection, complex regional pain syndrome or clinical signs of disturbed circulation (reduced capillary refill time >3 seconds) recorded in any group.

4.5: Paper V

30 patients (median age 67 [range 55-79]) completed follow-up. Of these patients 83% were retired, the dominant hand was treated in 70% and the small finger was the most commonly treated finger (61%).

Median TAED at baseline was 85 (IQR 60-115) and at 5 weeks median TAED had improved to 20 (IQR 0-40). During the COPM interviews, the patients identified 107 activity problems, 55 in self-care, 33 in leisure, and 19 in productivity. To wash self (n=21) and to put on gloves (n=19) were the 2 most commonly identified activity problems in the COPM interviews followed by shaking hands (n=8). Of the identified activities, 25 were unique to a specific patient. An improvement of ≥3 points occurred in 72% of activities for performance and 67% of activities for satisfaction; the corresponding value for improvement of ≥2 points was 86% and 81% for performance and satisfaction, respectively. The median COPM score for performance was 4.4 points (IQR 3.4-5.5) and for satisfaction 3.6 points (IQR 2.6-

5.5). At 5 weeks this had improved to 9.0 (IQR 8.0-10.0) for performance and 9.2 (IQR 8.0-10.0) for satisfaction. Median QuickDASH scores were 13.6 (IQR 2.3-20) at baseline and 2.5 (IQR 0-9.1) at 5 weeks.

The Responsiveness (Cohen's d) for COPM was 2.6 (95% CI 1.9-3.3) compared to 0.6 (95% CI 0.1-1.1) for the QuickDASH.

4.6: Paper VI

As *paper VI* is an ongoing study no final results are yet available. Phase 1 of the study has been completed and a questionnaire has been developed after several expert group meetings and patient feedback. The questionnaire starts with 2 questions, regarding hand dominance and which hand is affected. This is followed by 68 items regarding activity limitations with 5 response options ranging from "no difficulty" "to unable to perform" as well as the choice to select not applicable. This is followed by 11 items regarding symptoms such as pain and 6 items inquiring about topics such as self-confidence and satisfaction. These 17 items have response options ranging from "not at all" to "very often", or from "very satisfied" to "very dissatisfied". Finally, the questionnaire is concluded with an open question (similar to the COPM) allowing patients to add and rate up to 3 additional activities that they find difficult to perform with the same response options as for the activity limitations described above.

Phase 2 has commenced, and patient recruitment began in June 2023 and is now ongoing with more than 250 patients recruited.

Chapter 5: Discussion

5.1 Long-term outcomes and the definition of recurrence

As Dupuytren disease cannot be cured, the disease will at some point recur. Thus, when informing patients about expected treatment outcome, it is essential to have knowledge regarding not only short-term outcomes but also long-term outcomes. Still, the definition of recurrence in Dupuytren disease has proved difficult to establish [60]. In a study by Kan et al. an expert group proposed that recurrence should be defined as worsening of contracture in a treated joint, by at least 20° from the 6-week follow-up [61]. In *Paper* I this definition of recurrence after collagenase injection was used in a mixed-joint cohort, demonstrating a 5-year recurrence rate of 17% for MCP joints and 25% for PIP joints. While there are few published prospective long-term follow-up studies after collagenase, 2 RCTs have published 5-year data. In their RCT comparing collagenase with PNF for MCP joint contractures, Byström et al. report recurrences in 56% of successfully treated joints [105]. This is considerably higher than in *paper I* but comparing the results of the 2 studies is difficult. First, in the study by Byström et al. only MCP joints were eligible for treatment whereas in *paper I* all joints were eligible. Second, previous treatment was an exclusion criterion in the study by Byström et al. but not in *paper I.* And finally, the definition of recurrence used in that study was joint contracture ≥20° in a successfully treated joint, which is different from that used in *paper* I. The CORDLESS study has also published 5-year data with recurrence rates of 39% and 66% for MCP and PIP joints, respectively [59]. As CORDLESS used the same definition of recurrence (contracture worsening by at least 20°) as in *paper* I, these data are easier to compare. One explanation for the lower recurrence rates shown in *paper I* could be the modified injection technique as compared to the original method used in CORDLESS [49, 59]. The distribution of treated joints and fingers as well as the number of previously treated joints in CORDLESS is also unclear. Another contributing factor may be that since its introduction, all patients treated with collagenase at the study center were treated by the same surgeon, who consequently gained considerable experience.

In *paper II* actual recurrence rates could not be calculated because no short-term follow-up measurements were available for the surgical cohort. Instead, the proportion of patients with a current contracture of >20° was calculated, showing a current contracture in 19% of MCP and 48% of PIP joints in the fasciectomy cohort

and 19% of MCP and 33% of PIP joints in the collagenase cohort. As the collagenase cohort was the same in *papers* I & II (but with more patients having attended follow-up in paper I) this further highlights the impact the definition of recurrence can have on reported outcome. The definition of current contracture in *paper* II is similar to the definition of recurrence used in the study by Byström et al. and is a plausible explanation for the considerably higher recurrence rates reported in that study than would have been the case if the consensus-based definition had been used [61, 105].

Despite that surgical fasciectomy has been and still is the most common treatment for Dupuytren disease, few prospective long-term studies have been published. To date, two long-term (5 years) follow-ups of RCTs comparing surgical fasciectomy with PNF have been published. Van Rijssen et al. primarily defined recurrence as worsening of TED by 30° but redefined their definition as extension deficit ≥ 20° in a successfully treated joint (0-5°). With this new definition, they reported recurrence in 5.3% of MCP and PIP joints [97]. Selles et al. used the consensus-based definition of recurrence in their study and reported recurrences in 33% of MCP joints and 44% of PIP joints [136]. Although *paper II* does not use the term recurrence, the results are similar to those presented by Selles et al. while the recurrence rates reported by Van Rijssen is considerably lower. One reason for the higher number of patients with at least 20° of contracture in *paper* II may be the use of AED rather than PED. Another reason may be that both van Rijssen and Selles only included primary Dupuytren and not recurrent disease [97, 136]. As recurrent disease is generally more difficult to treat, another explanation for the higher number of joints with current contracture may be that *Paper II* also included patients with recurrent disease [155].

In addition to the studies mentioned above, two recent RCTs have evaluated surgical fasciectomy and collagenase regarding recurrence with follow-up time ≤2 years [135, 142]. Räisänen et al. reported recurrences, defined as reintervention within 2 years, in 1% of fasciectomy-treated patients and 10% of collagenase-treated and PNF-treated patients [135]. While reintervention is a well-defined definition of recurrence, it is not a measure of all recurrences. Because of the longer recovery and higher risk of complications after surgical fasciectomy, the threshold for reintervention is lower after minimal invasive treatments than it is after surgical fasciectomy, both on the part of the patient and the surgeon. While this results in limited comparability of the recurrence data, it is important to take this aspect into account when comparing cost-effectiveness of different treatments. Dias et al. defined recurrence (similar to Kan et al. [61]) as worsening of PED ≥20° in the reference joint between 3-month and 1-year follow-up examinations [142]. In their study Dias et al. reported recurrences in 13.8% in the fasciectomy group and 17.2% in the collagenase group with an estimated risk difference of 4 percentage points between the groups (95% CI -3.7 to 11.7) [142]. However, in that study the recurrence data was calculated on less than 60% of the treated patients in each group, thus adding uncertainty to the results [142]. Furthermore, despite that the

original proposed definition was that recurrence should be reported as worsening of contracture between 6 weeks and 1 year, recurrences often take more time to develop [136, 156], highlighting the need for long-term follow-ups.

Finally, an important factor when considering recurrence is that regardless of definition, it is the patients' activity limitations that is important. In a long-term follow-up of collagenase-treated patients, a joint contracture of 30°-60° was found as a threshold to be troublesome [157]. The table top test is often used as a simple indication of when treatment for Dupuytren disease may be warranted. As the table top test is typically positive at around 30° of extension deficit patients that meet the recurrence endpoint in studies, may still not fulfil treatment indications based on the table top test. Therefore, it is important to explain to patients that recurrence does not necessarily require retreatment when informing about expected treatment outcomes.

5.2. Treatment of recurrent disease

It has been established that both fasciectomy and the minimal invasive treatments are effective options for primary disease. However, because of the uncurable nature of Dupuytren disease, the need for treatment of recurrent disease is obvious. Thus, the question to be answered is, which is the optimal treatment for recurrent disease? Surgical fasciectomy has been the primary treatment for many years and has proven effective but is associated with complications [95, 122]. While both collagenase and PNF treatments can be repeated, the time between treatments has been shown to decrease with repeat PNF [117, 125, 127]. Thus, it has been shown that all available treatments are suitable when treating recurrent disease. However, there is still no consensus regarding whether surgical fasciectomy after previous collagenase is associated with increased risks [119, 120, 158]. Regarding PNF, there are few prospective studies investigating the safety in joints previously treated with fasciectomy or collagenase. But it has been suggested that if the patient fulfills treatment indications and have no severe scarring or neurovascular injury it can be a suitable treatment [122]. Furthermore, it remains to be established which treatment is most effective and most cost effective when treating recurrent disease. In *paper IV* 1-year outcomes for collagenase and surgical fasciectomy when treating recurrent disease are presented. As expected, severe adverse events were more common in the surgical group and there was a higher (worse) mean QuickDASH score at 3 and 6 weeks in the surgical group which is also reasonable due to the more invasive nature of surgical fasciectomy. Regarding contracture reduction and all other PROMs no differences were seen between the 2 groups supporting that short-term outcomes are similar for the 2 methods. These results with similar contracture reduction but better QuickDASH scores support that collagenase injection can be an effective treatment for recurrent disease with fewer complications and less activity limitations than surgical fasciectomy. However, it has previously been

shown that recurrences often do not occur until after 1 year [136, 156]. The future 2-year and 5-year outcomes will contribute with more information regarding recurrence as well as regarding overall treatment costs for the different treatments.

5.3 Patient-reported outcomes

As the impact of Dupuytren disease cannot be measured only in degrees or as recurrences, PROMs play a pivotal part when assessing treatment outcome and when comparing different treatments. It has previously been shown that there is a large variation regarding the use of PROMs although the DASH and QuickDASH have been most commonly used [47]. As it has been suggested that the DASH/QuickDASH are not optimal PROMs for Dupuytren disease mainly because of weak correlation with change in contracture [70], the introduction of the Dupuytren-specific PROMs was a step forward in Dupuytren research. Despite this, it has been obvious that both the URAM and the SDSS have failed to show superiority compared to other PROMs. So, what is the difficulty with Dupuytren PROMs? One aspect that appears to be harder than expected is to provide a PROM that is relevant for the patients. In *paper V* patients reported 107 activity limitations, which clearly shows the difficulty of capturing patients' activity limitations in a fixed-item PROM. While it is not possible to include over 100 items in a fixed-item PROM there are alternatives. One alternative is to use more general items that are open for interpretation as in the SDSS. Another option is to use patient-specific PROMs such as the COPM. In *paper V* the COPM was shown to be highly responsive in measuring change in activity limitations following treatment for Dupuytren disease. It is possible that patient-specific PROMs are the most suitable options for use in Dupuytren disease. However, as mentioned in *Paper V* the COPM is time-consuming and thus not practical to use in daily clinical practice. *Paper VI* describes the rationale behind the development of a new Dupuytren-specific PROM using modern methodology including IRT. As the study is ongoing and no final PROM has been developed, it is not yet known how it will perform. However, should it perform well a future possibility could be that the Dupuytren-specific PROM is suitable for clinical practice and large studies.

5.4 Methodological quality and risk of bias

With the introduction of collagenase, research on Dupuytren disease increased markedly. In 2009 Hurst et al. published their study in the New England Journal of Medicine. Today when searching PubMed for "Dupuytren disease" and limiting the search for publications until 2023 the search yields 4273 results. While it is reasonable

to assume all these publications may not be on Dupuytren disease, it is interesting to note that 45% of these have been published between 2009 and 2023. While it is beneficial that more studies emerge, it is important to remember that all studies are susceptible for bias and methodological errors. The matter of risk of bias in Dupuytren research has been approached in previous reviews including the Cochrane review with mostly moderate to high risk of bias scores [9, 159, 160]. While RCTs are generally considered as the methodological gold standard when evaluating treatments, there are generally few Dupuytren-related RCTs published. In *paper III* the RCTs comparing PNF with collagenase injection are reviewed for methodological quality and risk of bias. As shown in *paper III* despite being RCTs all the reviewed studies showed high risk of bias. Still as all reviews that assess risk of bias are susceptible to inter-observer differences it is not surprising that the results may differ between *paper III* and previously published reviews [9, 159, 160]. The results do however suggest that RCTs alone may not be optimal to compare treatment methods for patients with Dupuytren disease. The most obvious reason for this is that the nature of surgical treatments makes them susceptible to bias. For instance, when comparing surgical fasciectomy with either PNF or collagenase neither the patient nor the surgeon can be blinded. Thus, only the outcome assessors can be blinded as in *Paper IV* and the RCT by Strömberg et al. [51]. However, as described in *paper IV* it is not certain that the outcome assessors can be blinded if surgical fasciectomy is compared to PNF or collagenase due to scarring. Furthermore, since RCTs all have very specific inclusion and exclusion criteria, the generalizability of the results are limited to only patients that fit these criteria. One such example is that 3 of the RCTs comparing PNF with collagenase only assess MCP joints, thus limiting the generalizability of the results to this joint [50, 51, 140]. A second reason for why RCTs alone may not be suitable for comparing treatments for Dupuytren disease is that the study design introduces selection bias by default. When treating Dupuytren disease the treatment method is decided by adding together several factors such as joint involvement (with PIP joints more difficult to treat) skin involvement, heredity, scarring etc. Thus, as patients involved in an RCT must be suitable for both trial treatments, selection bias is introduced. With the effect being that a contracture that may not need fasciectomy may still be randomized to that, possibly affecting outcome and also the generalizability of the results.

5.6 The role of collagenase and effects of its withdrawal

With the introduction of collagenase in 2010 a simple and less invasive treatment than surgical fasciectomy was made available for patients. Today collagenase is considered one of the standard treatments for Dupuytren disease and a recent survey-based study in the USA established that, for patients suitable for all treatments, most surgeons would use collagenase [116]. While that the study has its

flaws, mainly a response rate of less than 25%, it still gives interesting information. One important effect of collagenase is that it raised the awareness for Dupuytren disease. A previous study showed that the number of patients seeking healthcare for Dupuytren disease increased by 56% and the number of Dupuytren procedures increased by 36% in the years around the introduction of collagenase [161]. On the same topic, it is likely that collagenase played a substantial role in the increase of Dupuytren research seen in the last 15 years. The introduction of collagenase has also played a substantial part in the shift from surgical fasciectomy toward less invasive treatments [26, 133, 161]. An interesting aspect is that the shift from fasciectomy to minimal invasive treatments seems to be mostly toward collagenase. In 2 studies of treatment trends in the USA the number of PNF treatments remained unchanged except for patients in the elderly population with ≥4 comorbidities among whom PNF increased [133, 161]. The reason why the percentage of PNF remained unchanged despite the introduction of collagenase is uncertain but a possible reason for the increase of PNF in the elderly population may be the publication of the RCT comparing PNF with surgical fasciectomy by Van Rijssen et al. [97]. As the risks of serious adverse events are lower for minimal invasive treatments, a possible contributing aspect for the increase in Dupuytren procedures may be a change in treatment threshold allowing patients treatment for simpler contractures that may not yet have been eligible for fasciectomy.

As collagenase was withdrawn in all non-US markets in 2020, the question is how this will affect Dupuytren treatment in these countries. As patients are now more aware of the possibility of treating Dupuytren disease it is possible that the number of patients seeking healthcare for Dupuytren disease will remain constant. Thus, there needs to be a shift in treatment trends to account for the patients previously treated with collagenase. For primary disease many of these patients will probably be adequately treated with PNF, but for those with recurrent disease many cases may not be suitable for PNF. However, as the results shown in *paper IV* indicate, patients with recurrent disease randomized to collagenase had similar outcome as those treated with surgical fasciectomy at the 1-year follow-up. In Sweden the number of surgical fasciectomies have increased after the withdrawal of collagenase, while the number of PNF procedures have increased in the same period (Figure 11). Although this trend coincides with the withdrawal of collagenase, it is not certain that this is the sole reason for the increase in surgical fasciectomy and PNF. One explanation for the increase in surgical fasciectomy could be that surgeons have gained knowledge from experience and studies such as *paper I* regarding which contractures may be less suitable for minimal invasive treatment [53]. Also as the withdrawal of collagenase coincided with the covid pandemic and its effects on the Swedish healthcare system, the number of procedures during that period is probably not representative. Furthermore, there are probably inconsistencies in the reporting as for instance the RCT by Scherman et al. was ongoing during 2012 but no procedures were reported using the procedure code for PNF. However, while the effects are still uncertain, it is undeniable that the

withdrawal of collagenase will have impacts on future Dupuytren treatment in the affected countries and, with more fasciectomies, treatment costs are likely to increase [144].

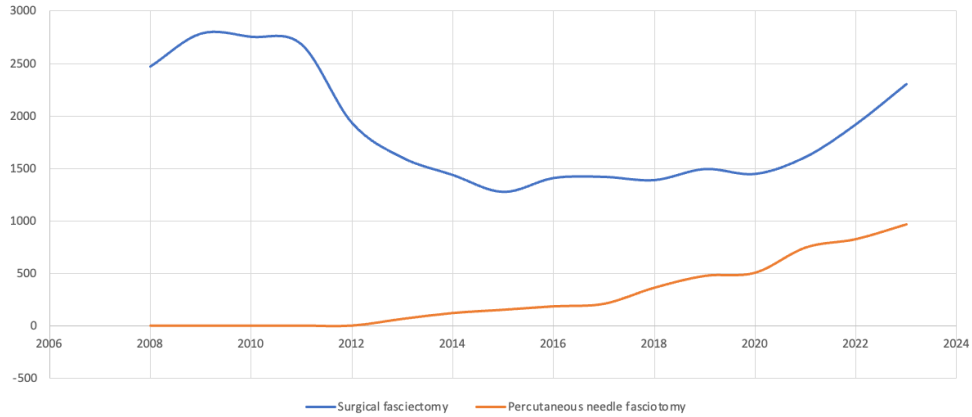


Figure 11. Data from the Swedish National Board of Health and Welfare (Socialstyrelsen) regarding the number of surgical fasciectomies (reported as NDM19) and percutaneous needle fasciotomies (reported as TND03) in Sweden 2008-2023 [162]

Chapter 6: Strengths and limitations

6.1 Overall

The main strength of this thesis is the use of several methodologies to study different aspects of Dupuytren disease. The thesis also includes the first randomized controlled trial comparing collagenase injection with surgical fasciectomy for recurrent Dupuytren disease. Furthermore, the thesis includes both a long-term prospective follow-up study on collagenase as well as a long-term comparative cohort study comparing collagenase injection with surgical fasciectomy for Dupuytren disease. A limitation of this thesis is that the clinical studies involve collagenase and fasciectomy but do not assess the comparative efficacy of PNF. However, several studies of that character have been published and this thesis includes a systematic review studying the risk of bias and methodological quality of some of these studies. While PROMs are a large focus of this thesis, no Dupuytren-specific PROMs were used in any of the studies. Nevertheless, one of the papers included in the thesis is a protocol for an ongoing study that aims to develop a new Dupuytren-specific PROM.

6.2 Paper-specific

Paper I

The prospective design combined with the long-term follow-up time of five years is the main strength of this study. The large number of patients together with the high percentage of patients completing follow-up are also strengths of the study that enhance generalizability.

However, due to the long follow-up time, the baseline and the 5-year measurements were not performed by the same assessor. Also, the 5-year measurements were performed by 2 assessors due to logistical reasons. Since it has previously been established that measurements may vary depending on the assessor this limitation may impact study outcome [58]. Furthermore, the QuickDASH was used at the 5-year follow-up despite being a general upper extremity PROM rather than a Dupuytren-specific PROM. Since no pre-treatment QuickDASH scores were

collected, the change over time in QuickDASH score was not possible to calculate. For the same reason we could not include pre-treatment QuickDASH scores as a variable in the analysis to identify risk factors for recurrence.

Paper II

As *paper II* utilized the same collagenase cohort as *Paper I,* some of the strengths and limitations in that paper also apply to *Paper II*. Still, there are some strengths and limitations that are more specific for this study. One such strength is the long-term comparison between collagenase and surgical fasciectomy with a high percentage of patients in both cohorts completing follow-up, as well as the relatively large cohorts. Also, the procedures in the surgical cohort were performed by several experienced surgeons which increases the generalizability of the outcomes. However, as the 62 hands included in the study were treated by 8 surgeons, the number of procedures per surgeon were few. A limitation in the study's design is that the surgical cohort was a retrospective cohort. Thus, missing data such as early postoperative measurements precluded analyzing and comparing the cohorts regarding recurrence. Also, since the study was not randomized, there is a risk of selection bias resulting in more difficult contractures in the surgical cohort (more severe pre-treatment PIP joint contractures and a higher proportion of previously treated patients).

Paper III

In this study the main strengths were the use of validated tools, namely the RoB2 and the modified JADAD scale. Although the assessments were independently performed by two researchers, one of whom was blinded to the origin of the studies, interobserver variability could explain why the results differ from those of similar reviews [160]. Also, we only searched 2 databases and additional studies beyond those included may be missed. Finally, while not the aim of the study, the choice to not include any meta-analysis of study outcomes may still be considered as a possible limitation since this reduces the knowledge gained from the study.

Paper IV

The most obvious and important strength of *paper IV* is that it is the first RCT study that compares collagenase and surgical fasciectomy for recurrent Dupuytren disease. The inclusion of patients with contracture in both MCP and/or PIP joints is another strength that further increases the generalizability of the study outcomes. Also, the stratified randomization of the cohorts according to previous treatment (surgery or minimal invasive) as well as small finger involvement (a known risk for recurrence as also shown in *paper I*) to minimize the risk of these factors introducing

bias [53]. While the randomization was stratified according to previous treatments, we chose to stratify according to minimal invasive (collagenase or PNF) versus surgical fasciectomy. This proved to be a limitation since all patients previously treated with PNF were randomized to the same cohort. Furthermore, while the RCT design is (correctly) considered a large benefit when designing comparative studies, RCTs are also subject to bias. One such bias that always follows the design is that patients must be eligible for both trial treatments. A possible implication may be that some very severe contractures deemed to be appropriate only for surgery may be excluded from the study. In our study as well as most surgical trials, blinding is difficult, while the surgeon performing the procedure cannot be blinded to the type of procedure, it is possible to blind the follow-up assessments. However, the use of thin cotton gloves to ensure blinding in *paper IV* may not have ensured blinding in all cases, thus adding another limitation to the study.

Paper V

The main strength of this study was that both the COPM and the QuickDASH were used in a relatively large sample of patients considering the time-consuming nature of the COPM. While use of the QuickDASH can be considered a limitation, we chose to use the QuickDASH since it was the most commonly used PROM in Dupuytren disease at the time of the study and no Swedish, disease-specific PROMs were available at that time [54]. Another possibly more important limitation of this study was that any potential presence of contracture in other fingers of the same or the other hand were not taken into consideration when conducting the analyses. Also, it is possible that the first COPM interviews made patients more aware of any activity limitations at the time of the second interview.

Paper VI

As this study aims to develop a new Dupuytren-specific PROM the main strength is the use of IRT-based methodology, which has advantages compared to CTT-based methods. Other strengths of the study include the experienced expert group that developed the questionnaire in phase 1 and the international multi-center setting. However, a possible limitation could be that the original questionnaire in phase 1 was developed at a single study center. Furthermore, the administration of the questionnaire before the patient's doctor appointment could risk that patients may exaggerate their symptoms or activity limitations.

Chapter 7: Conclusions

I. Five years after treatment with collagenase, 3 of 4 joints did not develop recurrence. A worse baseline joint contracture as well as treatment of the small finger were independent risk factors for recurrence of PIP joint contracture.

II. Patients treated with both collagenase and surgical fasciectomy show significantly improved joint contractures at 5 years compared to baseline but contractures of ≥20° are common 5 years after both treatments.

III. Published RCTs comparing collagenase injection with PNF for Dupuytren disease have a high risk of bias and low methodological quality.

IV. Surgical fasciectomy and collagenase injections are both safe and effective treatment options for recurrent Dupuytren disease with similar outcomes at 1 year. Patients treated with collagenase have less activity limitations than those treated with fasciectomy up to 6 weeks after treatment.

V. For patients with Dupuytren disease, the COPM has significantly higher responsiveness than the QuickDASH. The findings highlight the possible potentials of individualized PROMs in Dupuytren research and clinical practice.

VI. This is an ongoing study aiming to develop a new Dupuytren-specific patient reported outcome measure to contribute to future advancement of Dupuytren treatment and research.

Chapter 8: Future perspectives

While the introduction of collagenase has led to several advances in the treatment of Dupuytren disease much remains to be learned. With the large number of studies and research on the subject of Dupuytren disease the need for high-quality research has become clear. To enable this, it is crucial to achieve a consensus regarding the assessment and reporting of outcomes and, most importantly, adherence to the consensus regarding the definition of recurrence to allow comparison across studies.

With the increased knowledge about the contributing genetics of Dupuytren disease it is possible that new targeted treatments can be developed. Such research is currently ongoing [91], and it is possible that these treatments will be available in the future, allowing doctors and patients the means to prevent the progress of the disease. However, until such new treatments become available it is important to continue to improve current treatment methods. While the knowledge regarding long-term outcomes after treatment for Dupuytren disease has increased in recent years, future studies with follow-up longer than 5 years are needed as well as further studies regarding treatment of recurrent disease. To be able to determine which treatment method is the most cost effective, economical aspects will also need to be included in these studies. This should include not only direct treatment costs but also indirect costs such as loss of income, costs of repeat treatments, and treatments for recurrence over a specified time period. To increase generalizability of future studies, a combination of pragmatic RCTs with patients of different disease severity as well as high-quality long-term follow-ups would be important. The development of a nationwide (or international) Dupuytren register would further improve future Dupuytren research. Allowing surgeons to enter patient data including standardized measurements of ROM, potential risk factors, and PROM data from responsive validated PROMs would facilitate performing large studies that are otherwise difficult to perform. Furthermore, the development of nationwide guidelines regarding optimal treatment methods for different stages of disease that also incorporate risk factors would simplify treatment decisions for clinicians while also ensuring more equal healthcare for patients with Dupuytren disease.

Finally, due to the withdrawal of collagenase from non-US markets, studies in the next few years will likely show how treatment trends in these countries changed after the withdrawal of collagenase and what effects the withdrawal had on the incidence of treatments, recurrences as well as on treatment costs.

Populärvetenskaplig sammanfattning

Dupuytrens sjukdom även kallad vikingasjuka, angriper palmarfascian, som är en bindvävshinna i handflatan. Detta orsakar en ökad kollagenproduktion som i sin tur leder till förhårdnader och strängar i handflatan. Dessa strängar kan med tiden skrumpna varvid en svårighet att räta ut fingrarna (så kallade kontrakturer) uppträder. Sjukdomen är vanligtvis smärtfri men kontrakturer kan orsaka problem av varierande grad i vardagen, då sträckdefekterna kan påverka möjligheten att greppa föremål samt försvåra aktiviteter som att skriva på dator, tvätta sig eller att ta på sig handskar.

Även om icke kirurgiska metoder såsom ortoser och strålning prövats, har behandlingen för Dupuytrens sjukdom tidigare framförallt varit operation och då oftast så kallad fasciektomi där kirurgen strävar efter att avlägsna all sjuk vävnad. Medan fasciektomi ofta är framgångsrik avseende att åtgärda kontrakturer i fingrarna, är metoden samtidigt associerad med en risk för allvarliga komplikationer samt med en lång läktid och återhämtning. Då Dupuytrens sjukdom inte går att bota finns alltid en risk för återfall (recidiv), vars behandling är associerat med än högre risk för komplikationer. Som alternativ till fasciektomi har två minimalinvasiva metoder ökat i popularitet. Dels så kallad perkutan nålfasciotomi där Dupuytrenssträngen delas med en kanyl för att möjliggöra uträtning av fingret, dels en läkemedelsbehandling där ett kollagenas injiceras i Dupuytrenssträngen och löser upp denna varefter fingret någon dag senare kan rätas ut. Dessa metoder har båda visats ha lägre risk för allvarliga komplikationer än fasciektomi, men recidiv är vanligare efter nålfasciotomi än efter fasciektomi. Samtidigt har kollagenas visats ha bra korttidsresultat och även visats kunna användas för att behandla recidiv. Vid utvärdering av sjukdomsförlopp och behandlingsresultat hos patienter med Dupuytrens sjukdom används ofta patientrapporterade utfallsmått (PROMs) som komplement till kliniska utfallsmått. I dagsläget saknas dock fortfarande kunskap gällande långtidsresultat efter kollagenas, och det finns i dagsläget inga studier som jämför kollagenas med kirurgi vid behandling av recidiv. Därutöver har det visats att befintliga PROMs inte är så effektiva på att fånga upp förändringar i sjukdomsorsakade aktivitetsbegränsningar när ledkontrakturer i fingrarna förvärras eller förbättras.

I denna avhandling ingår sex delarbeten som studerar olika aspekter av Dupuytrens sjukdom. Delarbete I undersökte långtidsresultat (5-år) efter kollagenas. Delarbete II jämförde långtidsresultat (5-år) efter kirurgisk behandling och kollagenas.

Delarbete III var en systematisk litteraturöversikt som studerade metodologisk kvalitet och risk för bias (systematiska fel) i randomiserade kontrollerade prövningar som jämfört kollagenas med nålfasciotomi. Delarbete IV är en ettårs-resultat av en randomiserad kontrollerad prövning som jämför kirurgi med kollagenas vid behandling av recidiv efter tidigare behandlad Dupuytren. Delarbete V undersöker korttidsresultat efter kollagenas samt jämför 2 olika patientrapporterade utfallsmått (QuickDASH och Canadian Occupational Performance Measure [COPM] beträffande känslighet att upptäcka förändring i aktivitetsbegränsning efter behandling . Slutligen är delarbete VI ett studieprotokoll för en pågående studie som ämnar till att utveckla en ny Dupuytrenspecifik PROM.

Sammanfattningsvis har avhandlingen visat att återfall av Dupuytren är vanligt 5 år efter behandling med kollagenas. Att leder behandlade med såväl kollagenas som med kirurgi uppvisar förbättrad ledkontraktur vid 5 år även om ledkontrakturer över 20° var vanliga i bägge grupper. Därutöver visar ettårs resultaten från delarbete IV på att kollagenas kan vara ett alternativ vid behandling av recidiverande Dupuytrens sjukdom, men att längre uppföljning krävs för att se om effekten bibehålls över tid. Avhandlingen har också visat att risken för systematiska fel är hög i randomiserade kontrollerade prövningar som jämför kollagenas med perkutan nålfasciotomi, varför dessa ej bör stå som ensam grund vid utveckling av behandlingsriktlinjer. Avhandlingen har också visat att COPM har hög känslighet för förändring i ledkontraktur vid Dupuytrens sjukdom. Slutligen har arbetet med att utveckla en ny PROM som är specifik för Dupuytrens sjukdom påbörjats och än så länge har mer än 250 patienter inkluderats i studien.

Acknowledgements

Isam Atroshi – my main supervisor. You've supervised me for 7 years and all my progress during these years are thanks to your guidance. You've always been available, providing support and constructive feedback while also always expecting my best efforts in return. You've made me a better researcher as well as a better surgeon, thank you for everything.

Jesper Nordenskjöld – my co-supervisor. You've been there from the beginning. Providing guidance, support and feedback throughout all stages of my PhD studies and you were also the best clinical teacher I had during my residency.

Muhanned Ali – my co-supervisor. Always providing straight feedback, pointing out what needs to be improved while also giving encouragement and support**.** Thank you for all your support when writing this thesis.

Lars Dahlin – my mentor. During my fifth semester of medical school, you introduced me to both the research community as well as to Dupuytren disease. Whenever I needed your input or support you've always made time for me, despite your busy schedule. You inspired me to start my PhD studies.

Anna Lauritzson – my co-author in almost all my publications. Thank you for your clinical support and your help and input in all our studies.

Ingrid Isaxon, Maria Persson and **Stina Brodén** – occupational hand therapists. Without you, none of the studies in this thesis would be possible.

Ingela Ranebo – research nurse. Thank you for all your valuable feedback as well as helping me coordinate the studies in this thesis.

My friends and colleagues, especially Filip Sandberg, Louise Lindén and Sebastian Randahl – thank you for supporting me through all these years.

My parents and siblings – thank you for always being there for me.

Johanna Eckerdal – my amazing wife. You have encouraged me through all the years, taking care of our home, kids and always giving support. Thank you.

Elsa & Sigrid Eckerdal – my lovely daughters, now we'll have all the time in the world.

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