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Dupuytren's Disease: Etiopathogenesis, Clinical Manifestation, Types of Surgery, Surgery vs Conservative Treatment - Literature Review

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I. ABSTRACT

This literature review discusses Dupuytren's Disease, a fibroproliferative disorder characterized by progressive fibrosis of the palmar fascia leading to contracture of the fingers, mainly affecting the ring and little fingers. The context of this review is the significant impact of Dupuytren's Disease on hand function and quality of life in patients, as well as the challenges it poses in clinical management due to its complex aetiology and variable progression. The aim is to summarize the current knowledge of Dupuytren's Disease with a focus on its pathogenesis, treatment efficacy, and patient outcomes, with the intention of illuminating areas for further research and potential improvement in patient care.

Methodologically, the review pools and critically appraises studies from different databases, adhering to inclusion criteria to ensure relevance and rigor. These criteria include studies on genetic determinants of Dupuytren's Disease, cellular mechanisms, and treatment outcomes, as well as both surgical and conservative approaches.

Findings reveal a multifactorial aetiology involving genetic predisposition and environmental factors, with treatments ranging from invasive surgical options to non-invasive modalities that show varying efficacy in different patient groups. Surgical interventions, although effective for the present, carry a risk of recurrence and complications, whereas conservative treatments offer safer, although sometimes less durable, results.

The importance of this work lies in the comprehensive review of Dupuytren's Disease, which not only improves understanding of the complexity of the disease but also highlights the need for individualized treatment strategies. It highlights the critical balance between treatment efficacy and patient safety and advocates an integrated approach that takes into account the specific circumstances, disease stage, and lifestyle of the patient. This review calls for continued research into innovative treatments and early intervention strategies to improve prognosis and quality of life for patients while reducing the burden of Dupuytren's Disease on healthcare systems.

II. METHODOLOGY AND KEYWORDS

This literature review was conducted through a scoping search of electronic databases, including PubMed, Web of Science, Google Scholar, and Scopus, from May 2023 until March 2024. The search strategy was designed to capture all relevant literature about Dupuytren's Disease and ultimately compare surgical and conservative treatments. Keywords and MeSH

terms used in the search included „Dupuytren's Disease," „Dupuytren's Contracture," „Morbus Dupuytren," „surgical treatment," „conservative treatment," „pathophysiology," „genetic factors," „collagenase injections," „radiotherapy," „physical therapy," „treatment outcome," and „patient satisfaction."

A narrative synthesis approach was used to integrate findings from the included studies, with a focus on comparing the outcomes of surgical versus conservative treatments. Key themes were identified, and evidence was summarized to reflect the current understanding of treatment efficacy and patient outcomes in Dupuytren's Disease.

Table 1 Search strategy

Search items		
Dupuytren's Disease OR Dupuytren's Contracture OR Morbus Dupuytren AND surgical treatment AND conservative treatment AND pathophysiology AND genetic factors AND collagenase injections AND radiotherapy AND physical therapy AND treatment outcome AND patient satisfaction		
Inclusion criteria	**Exclusion criteria**	**Resources searched**
• English language • German language • Peer reviewed • Publication dates between 1959 and 2023 • Studies reporting on metrics such as effectiveness, recurrence rates, complications, and patient-reported outcomes	• Editorials • Articles not available in English • Articles not available in German	• PubMed • Web of Science • Google Scholar • Scopus

III. INTRODUCTION

Dupuytren's Disease (DD), a fibroproliferative disorder, has long intrigued and challenged the medical community. Characterized by the progressive thickening and shortening of the palmar fascia, this condition leads to irreversible flexion contractures of fingers, predominantly affecting the ring and little fingers. (1) The development and progression of this disease have an impact on hand function and quality of life, making its management highly important in clinical practice.

This literature review aims to examine various aspects of Dupuytren's Disease, starting with a comprehensive exploration of its causes and mechanisms. Understanding the genetic factors behind this condition is crucial for developing targeted treatments and identifying individuals at risk. The review will delve into research findings and theories that shed light on the diseases underlying mechanisms, including genetic predisposition, association with other medical conditions as well as cellular processes.

Following this, the review will shift its focus to the clinical manifestation of Dupuytren's Disease. It will cover the spectrum of symptomatic presentation, ranging from mild nodules and cords in the palm to severe contractures leading to functional impairment. The discussion will include an analysis of the disease's progression, variability in symptomatology among different populations, and the impact on patients' daily activities.

A significant portion of the review will focus on exploring the surgical options available for Dupuytren's Disease. Traditionally, surgery has been the mainstay of treatment for cases. The review will delve into procedures such as fasciectomy, dermofasciectomy, and needle aponeurotomy, discussing when they are recommended, how they are performed, their outcomes, and potential complications.

However, the core of this literature review will be an examination of the ongoing debate between surgery and non-surgical treatment approaches. In the years, there has been increasing interest in alternatives like collagenase injections, radiotherapy, and physical therapy. The central research question guiding this review is „In the management of Dupuytren's Disease, how do surgical treatments compare with conservative approaches in terms of efficacy, patient outcomes, and long-term benefits, and what implications do these findings have for optimizing patient-specific clinical care?" This question aims to untangle the complexities and subtleties involved in treating Dupuytren's Disease. Ultimately, it seeks to provide insights that can influence decision-making and improve patient care.

IV. ETIOPATHOGENESIS

Despite the occurrence of Dupuytren's Disease and its significant impact on patient's quality of life, there is still a lot to learn about its causes and development. In years, there has been an increasing recognition of the importance of understanding the intricate molecular processes involved in Dupuytren's Disease. This chapter aims to provide an examination of the genetic factors and heritability as well as the cellular and molecular mechanisms underlying this condition. Additionally, this literature review will explore the connections between

Dupuytren's Disease and other medical conditions, shining a light on the multifaceted nature of this condition.

Cellular and Molecular Mechanisms

Dupuytren's Disease is characterized by an interaction between genetic factors, cellular alterations, and biochemical signaling pathways, all of which contribute to its pathophysiology at the cellular and molecular level. Before studying the specific genetic factors, a general look into the pathophysiological mechanisms should be undertaken.

The central cellular players in Dupuytren's Disease are myofibroblasts, specialized cells that resemble both fibroblasts and smooth muscle cells. They express α-smooth muscle actin (α-SMA), allowing them to contract and contribute to the deformation of the palmar fascia. (2) According to Joel Walthall et al. (2023), the disease begins when nodules start forming in the palm. (3) The nodules consist of myofibroblasts and fibroblasts. These myofibroblasts are critical cells in the disease's pathogenesis and are characterized by their contractile actin microfilaments. (4) Walthall et al. describe that during the stage of growth, there is a concentration of myofibroblasts that organize themselves in a spiral pattern. As the disease progresses to the involution phase, fibroblasts become more aligned along the longitudinal axis of the hand, following lines of tension. In the residual phase, acellular cords are rich in collagen due to the activity of myofibroblasts. These cords are responsible for causing contracture deformities. (3) According to Walthall, the myofibroblasts connect with fibronectin and extracellular fibrils and mainly produce type III collagen within the matrix. The characteristic hand deformities observed in Dupuytren's Disease are a result of bands transforming into pathological cords caused by these myofibroblasts (see Figure 1).

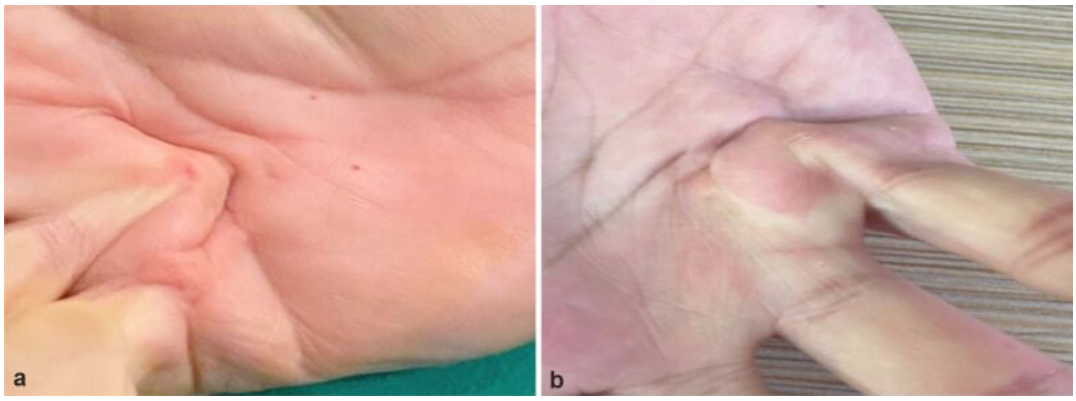

Figure 1: Digit in fixed flexion deformity; Trâmbiţaş et al., 2021 (5) CC BY-NC-SA 4.0

Recent studies also suggested that inflammatory cytokines play an important role in the underlying molecular pathophysiology of Dupuytren's Disease. (6)

Research conducted by Mark L. Wang et al. (2021) hypothesizes a correlation between advanced Dupuytren's Disease fibroproliferation and increased levels of circulating inflammatory cytokines. (7) The researchers found that patients with severe contractures showed significantly higher levels of circulating cytokines, including TNF-α, IL-2, and IL-12p70, compared to controls. IL-4 and IL-13 were also more frequently detected in Dupuytren's Disease patients. (7) The study establishes a specific cytokine profile in severe Dupuytren's Diseases, suggesting that elevated inflammatory cytokines may drive fibroproliferation.

These findings provide insights into the pathogenesis of Dupuytren's Disease and open new avenues for diagnostic and therapeutic interventions targeting the identified cytokines.

Another study by Liaquat S. Verjee et al. (2013) focused on understanding the transition of normal fibroblasts into myofibroblasts, the cells primarily responsible for the fibrosis seen in DD. (8) The researchers also found that affected tissue in Dupuytren's Disease contained macrophages and released various pro-inflammatory cytokines. The cytokines were produced by disaggregated cells from Dupuytren's Disease. (8) Verjee et al. describe that among the cytokines, TNF was uniquely effective in converting normal fibroblasts from the palms of Dupuytren's Disease patients into myofibroblasts. This process involves activating the Wnt signaling pathway, which will be described in the next chapter. The study enhances understanding of the cellular mechanisms leading to Dupuytren's Disease, specifically highlighting the role of TNF in promoting fibroproliferation and the development of myofibroblasts. The identification of TNF as a key factor in Dupuytren's Disease pathogenesis opens the door for new treatments, possibly involving localized TNF inhibitors, which could be more effective and have fewer side effects compared to systemic treatments.

Genetic factors and heritability

Understanding the genetic underpinnings of Dupuytren's Disease is crucial for several reasons. First and foremost, familial aggregation and population-based studies have consistently demonstrated a significant hereditary component, suggesting a genetic predisposition to the disease. (9) (10) By deciphering the specific genetic factors involved, clinicians and researchers can identify individuals at higher risk, facilitating early detection and intervention.

In the stages of studying Dupuytren's Disease, researchers focused on identifying specific areas of chromosomes linked to the condition. Dolmans et al. (2011) conducted a study using a genome-wide association study with 960 Dutch participants and found that nine loci are

involved in being predisposed to Dupuytren's Disease. (11) Six chromosomal loci contained genes involved in the Wnt-signaling pathway, which are crucial in cellular processes such as proliferation and differentiation. (11) Dolmans et al. further investigated these genes, which include WNT4, SFRP4, WNT2, RSPO2, SULF1, and WNT7B. This suggests that aberrations in this pathway play a key role in the disease's fibromatosis process. The findings highlight the importance of common genetic variants in the disease's development, particularly in Northern European populations. Further genome-wide association studies (GWAS) have supported these findings, indicating that certain locations on chromosomes are significantly associated with the disease. For example, a large genome-wide association study by Michael Ng et al. (2017) also aimed to identify genetic variants associated with Dupuytren's Disease. (12) The study involved 3871 individuals from the United Kingdom. In their work, the authors were able to confirm the previous association with nine loci and the discovery of 17 additional variants with $p \leq 5 \times 10{-}8$ associated with Dupuytren's Disease. The study highlighted the significant role of the WNT signaling pathway in Dupuytren's disease pathogenesis, with a specific focus on SFRP4, a soluble WNT antagonist. Michael Ng et al. showed that the high-risk genotype at a key variant (rs16879765) showed decreased secretion of SFRP4, suggesting an imbalance in WNT signaling contributes to Dupuytren's Disease fibrotic phenotype.

Another important systematic review and meta-analysis conducted by Nader Salari et al. (2020) aims to estimate the global prevalence of Dupuytren's Disease. (13) The study presents an extensive analysis of the global prevalence of Dupuytren's Disease, highlighting its variability across different regions and populations. The occurrence of Dupuytren's Disease was discovered to differ depending on the area and demographic variables, like age and gender, according to Salari et al. European populations exhibited higher rates of prevalence.

In summary, Dupuytren's Disease appears to be influenced by genes, indicating its polygenic nature. Another comprehensive study conducted by Richard Ågren et al. (2023) focused on identifying genetic variations associated with Dupuytren's Disease and underlines the previous findings. This study sheds light on an aspect of evolution, showing how genetic characteristics passed down from Neanderthals still influence the health of modern humans. (14) It presents evidence that certain genetic factors associated with Dupuytren's Disease can be traced back to our Neanderthal ancestors, providing a perspective on the origins and development of this condition. The research findings provide insights into the nature of Dupuytren's Disease, indicating that the genetic foundation of the disease is influenced not only by recent genetic variations in humans but also by ancient inherited genes. This discovery has the potential to

expand our understanding of the aspects involved in Dupuytren's Disease and may have implications for studies in evolutionary medicine and treatment approaches for this condition.

Association with other risk factors

Dupuytren's Disease is not an isolated medical phenomenon. Its occurrence has been correlated with several other medical conditions, suggesting a complex interplay between genetic, systemic, and environmental factors. This chapter aims to explore and elucidate the associations between Dupuytren's Disease and other risk factors, contributing to a more comprehensive understanding of its etiology and implications for patient care.

1. Diabetes Mellitus

Dupuytren's Disease has a well-established association with Diabetes Mellitus, particularly type II diabetes. (15) A study from Sandhya Ganesan et al. (2023) utilized the TriNetX Research Database and retrospectively analyzed the prevalence of Dupuytren's Disease among patients with diabetes mellitus (DM) from 2010 to 2020. (16) The focus was on comparing the prevalence between different diabetes types, namely type 1 (T1DM) and type 2 (T2DM), and assessing the influence of hemoglobin A1c (HbA1c) levels and anti-diabetic medications (insulin vs. metformin) on the prevalence of Dupuytren's Disease. The study revealed a significantly higher prevalence of Dupuytren's Disease in patients with T2DM compared to those with T1DM. This suggests a closer association of Dupuytren's Disease with adult-onset diabetes. (16) Ganesan et al. also found that there was a notable difference in the prevalence of Dupuytren's Disease based on the type of diabetes medication. Patients on insulin (typically indicative of more advanced diabetes management) showed a different prevalence rate compared to those on metformin. (16) Furthermore, the research showed that Dupuytren's Disease prevalence varied with the diabetic status as indicated by HbA1c levels. Patients with HbA1c levels within the diabetic range exhibited a different prevalence of Dupuytren's Disease compared to those with prediabetes or uncontrolled diabetes. (16) These findings underscore a complex relationship between Dupuytren's Disease and DM, potentially linked to the biochemical changes associated with diabetes, such as the accumulation of advanced glycosylated end products (AGEs). This research contributes significantly to the understanding of Dupuytren's Disease association with diabetes, offering insights that could guide future investigations and improve patient care strategies for those suffering from both conditions.

2. Alcoholism and Smoking

The relationship between alcoholism or smoking and Dupuytren's Disease (DD) is supported by multiple epidemiological studies. A recent randomized study by Zifeng Wang et al. (2023) utilized a two-sample Mendelian randomization (MR) approach to investigate the potential causal relationships between smoking and alcohol consumption and the risk of developing Dupuytren's Disease. (17) Key findings include a significant causal relationship between alcohol consumption (quantified as drinks per week) and an increased risk of Dupuytren's Disease, with an odds ratio (OR) of 2.948 (95% CI: 1.746–4.975, P = 5.16E-05) according to inverse variance weighted (IVW) MR analysis. No causal link was established between smoking-related behaviors and DD. Sensitivity analyses using methods such as MR-Egger, robust adjusted profile score (RAPS), weighted median (WME), and simple median (SME) supported these conclusions, indicating robustness in the results.

Further analyses explored the interactions between smoking and alcohol consumption, using bidirectional MR to examine their interplay. Multivariate MR analyses were conducted to distinguish the independent effects of smoking and drinking on Dupuytren's Disease, revealing that the causal effect of alcohol consumption on Dupuytren's Disease was independent of smoking behaviors.

The study concludes that alcohol consumption is a causative factor for Dupuytren's Disease, marking a significant advancement in understanding the disease's etiology and suggesting that reducing alcohol intake could serve as a primary prevention strategy for DD. However, it found no causal relationship between smoking behaviors and DD. These findings were derived from a comprehensive analysis involving large-scale GWAS data and robust MR methodologies, offering a credible insight into the lifestyle factors contributing to DD risk.

This comprehensive analysis presents a clear causal link between alcohol consumption and Dupuytren's Disease, offering a new perspective on prevention strategies for those at risk. However, it finds no evidence of a causal relationship between smoking and DD, contributing to the ongoing debate and study of its complex etiology.

While the study presents significant insights into the relationship between alcohol consumption, it must be said that the MR analysis depends heavily on the strength and relevance of the selected instrumental variables (IVs) - in this case, specific single nucleotide polymorphisms (SNPs) associated with smoking and alcohol consumption behaviors. If these IVs do not accurately reflect the exposure or if they are associated with confounders, the MR estimates could be biased. Furthermore, the study does not explore the potential differences in causal relationships between men and women. (17) Given that lifestyle behaviors and the prevalence

of DD can vary by gender, this could be an opportunity to uncover more nuanced insights in future studies.

V. CLINICAL MANIFESTATION

The clinical manifestation of Dupuytren's Disease varies from stage to stage and has a significant impact on patients' quality of life. This chapter discusses the progression of the disease using a classification system that explains common symptoms and signs, such as nodules and flexor contractures of the fingers.

Overview of disease progression and staging system

Dupuytren's Disease progression varies and can range from mild to severe. It is characterized by several stages, first described by Luck in 1959. (18); (19)

The first stage is the nodular stage, which is marked by the formation of firm and sometimes tender nodules in the palm. At this stage, there is no bending or contracture of the fingers. (20)

The second stage is the proliferative stage, during which the nodules thicken and may form cords that extend from the palm into the fingers. During this stage, normal cells transform into myofibroblasts. (21) The skin on the palm may appear puckered or dimpled. During the involutional stage, the cords of tissue begin to contract, causing the fingers to bend towards the palm. In the residual stage, the contractures become fixed, and the fingers may be permanently bent towards the palm, which interferes with hand function and daily activities. (22)

The Tubiana staging system is another widely used method for classifying the severity of Dupuytren's contracture based on the degree of finger flexion contracture. This system categorizes the disease into stages by considering the sum of angles of joint contractures (metacarpophalangeal and proximal interphalangeal joints). (23)

Table 2: Staging system by Tubiana et al. (1968)

Stage 0	No contracture
Stage N	No contracture; presence of palmar nodule
Stage I	Contracture between 1 and 45 degrees
Stage II	Contracture between 45 and 90 degrees
Stage III	Contracture between 90 and 135 degrees
Stage IV	Contracture greater than 135 degrees

Common symptoms and signs

Dupuytren's Disease progressively affects the hands through a series of symptoms and signs that begin subtly and can advance to significantly impair hand function. (24) Dupuytren's Disease usually begins with the appearance of small, hard nodules in the palm of the hand, which may be sensitive at first but become painless over time. Along with these nodules, changes appear in the skin of the palm, such as puckered or dimpled. (25) As the Disease progresses, the skin may thicken and adhere to the underlying tissues.

Further, the nodules may become palpable cords under the skin that extend beyond the fingers. (26) These ropes are thickened fascia that can eventually lead to finger contracture (see Figure 2).

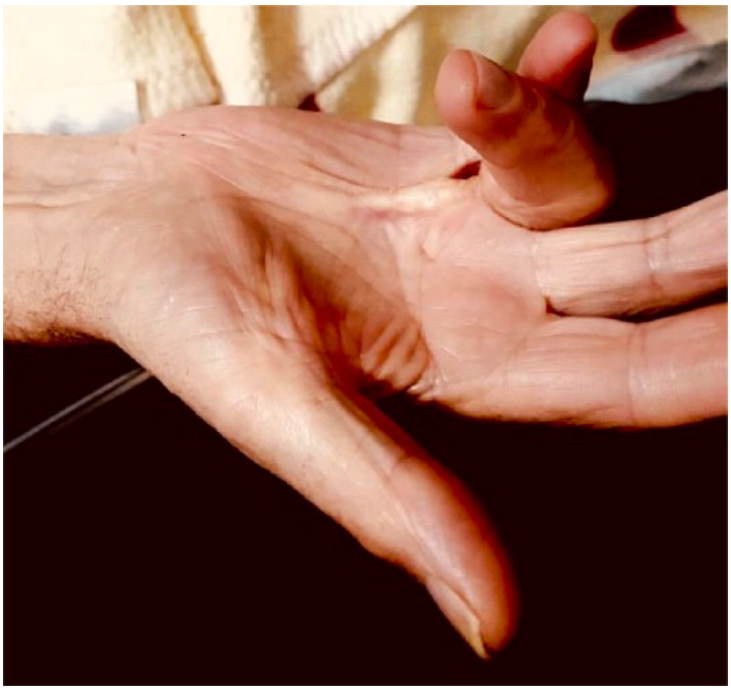

Figure 2: Metacarpophalangeal joint contracture > 30°; Grazina et al., 2019 (26) CC BY-NC 4.0

One of the main symptoms of Dupuytren's Disease is a contracture of one or more fingers, with the ring and little fingers being the most commonly affected. (27) Initially, this flexion may be mild and may not significantly affect the function of the hand. In advanced stages, Dupuytren's Disease can cause the fingers to permanently bend towards the palm, and the affected joints may become stiff due to disuse or severe contracture. (28) This restriction of movement and function can also lead to atrophy of the hand muscles, further reducing hand strength and dexterity. (29)

The progression of Dupuytren's Disease varies greatly from person to person. (28) Some may experience only mild symptoms for years, while others may rapidly progress to more severe forms of contractures. (30)

VI. CONSERVATIVE AND NON-SURGICAL TREATMENT APPROACHES

The treatment of Dupuytren's Disease presents a multifaceted challenge, and treatment strategies must be tailored to the severity of the disease, the patient's symptoms, and their effect on hand function and quality of life. Although surgical interventions are widely recognized for their efficacy in the advanced stages of Dupuytren's contracture, conservative treatment options play a role in the early management of the disease, symptom relief, and in cases where surgery is not immediately indicated or is not desired by the patient. Exploration of non-surgical treatment options is not only the cornerstone of comprehensive care but also provides valuable alternatives for patients who do not desire surgical treatment because of personal preferences, comorbidities, or concerns about the potential risks and recovery time associated with surgery. These non-invasive or minimally invasive approaches, including physiotherapy, injections, and splinting, have the advantage of being readily available and, in many cases, can be performed in an ambulant setting. Knowledge of the range of available conservative treatments is essential for healthcare providers to be able to offer tailored and patient-centered treatment plans. This allows patients to make informed decisions about treatment and to weigh up the benefits and limitations of each option.

Therefore, the aim of this chapter is to provide a review of different conservative treatment strategies and to assess their efficacy, benefits and limitations. By presenting a comprehensive picture of these options, the chapter highlights the importance of a holistic approach to the treatment of Dupuytren's contracture, improves patient education and facilitates shared decision making in clinical practice.

Physical therapy and splinting

Physical therapy for Dupuytren's Disease, especially in the early stages and after corrective treatment, has been investigated as a potential tool for symptom management, improving and assessing hand function, and possibly delaying disease progression. However, the efficacy of physical therapies is subject to limited and poorly validated studies, making it difficult to draw definitive conclusions about their effectiveness. The aim of a systematic review by Ball et al. (2016) was to assess the role and effectiveness of these non-surgical therapies in patients with early-stage Dupuytren's Disease, characterized by palmar nodules and little or no finger

contractures. (31) The review found that physical therapy was the most reliably evaluated non-surgical intervention, with objective measurements such as digital goniometric measurements of joint extension, hand girth, and grip strength. However, the small sample sizes of these studies mean that the evidence is insufficient to unequivocally determine their effectiveness. The results of the studies varied, with some showing improvements in hand function and others showing minimal or no change. For example, ultrasound treatment combined with physical mobilization and joint stretching improved digital joint extension in some patients, but the overall evidence was not strong enough to recommend ultrasound treatment as a standard treatment for early DD. (32) According to research by Ball et al. (33), the use of night splints and frictional massage has had some positive results (especially as a pre-operative holding measure for patients awaiting surgery), but the lack of larger and more rigorous studies means that these results should be interpreted with caution. Another study by Larson et al. (2008) observed the results of post-operative splinting. (34) The aim of this systematic review was to assess the effectiveness of post-operative splinting for Dupuytren's Disease. It included four studies with different designs and types of intervention, with follow-up periods ranging from 9 weeks to 2 years. The evidence for the effectiveness of static and dynamic splinting on extension deficit and hand function was found to be of poor quality and inconclusive. The review highlights the need for well-designed, randomized controlled trials to determine the true impact of splinting in the post-operative treatment of Dupuytren's contracture.

According to Ball et al. (31), the most important limitation of all the studies reviewed was the lack of a clear, universally accepted definition of early DD and the absence of standardized outcome measures. This lack of consensus makes it difficult to compare the results of the studies and to generalize the findings. In addition, the long-term effects and possible recurrence of symptoms after physiotherapy are still poorly documented, and further studies with longer follow-ups are needed.

Collagenase Clostridium histolyticum Injections

The exploration of collagenases dates back to the 1930s when scientists first observed the effects of filtrates from cultured Clostridium histolyticum on bits of horse Achilles tendons. (35) Nowadays, Collagenase Clostridium histolyticum (CCH) has gained significant traction as a treatment option for Dupuytren's contracture since its approval in 2010 by the United States Food and Drug Administration. (36) The usage of CCH, especially under the brand names Xiaflex or Xiapex in Europe, has been steadily increasing due to its benefits as a minimally invasive and non-operative treatment option. (37) Clostridium histolyticum collagenase

injections represent a significant advance in the non-surgical treatment of Dupuytren's Disease by targeting the collagen fibers that cause finger contractures. (38) This treatment is less invasive than traditional surgical approaches, allowing patients to recover faster and have a more comfortable procedure with comparable higher patient satisfaction levels. (39)
During the procedure the needle is inserted perpendicular to the cord (Figure 3):

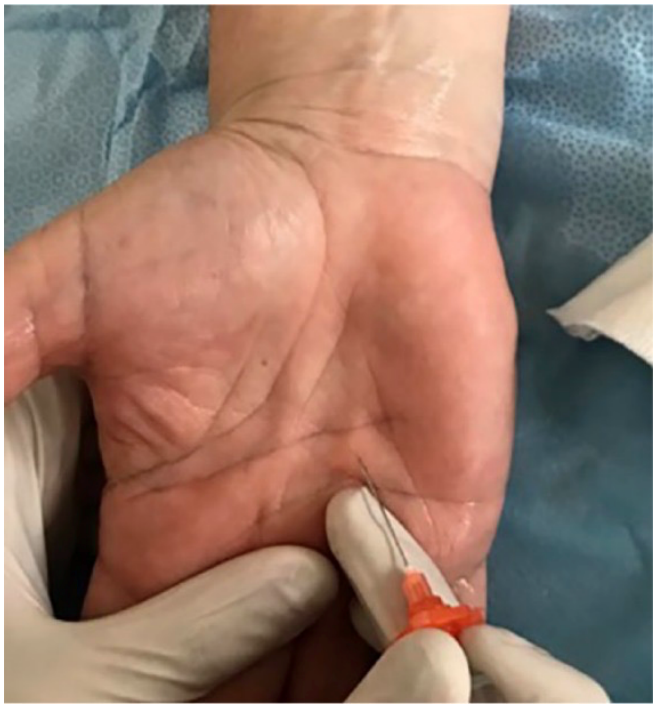

Figure 3: Photograph of collagenase injection; Grazina et al. 2019 (26) CC BY-NC 4.0

The injection directly disrupts the collagen fibers, improving finger mobility. (40) Further research and clinical trials continue to investigate the efficacy, safety, and long-term results of CCH injections, making this method a viable option for people with Dupuytren's Disease.
In a study conducted by Hurst et al. and published in the New England Journal of Medicine (2009) a pivotal phase 3 clinical trial, enrolled 308 patients in a randomized, double-blind, placebo-controlled multicenter study to evaluate the efficacy of CCH in reducing contractures associated with Dupuytren's Disease. (41) During the trial patients received up to three injections of CCH into the contracted collagen cord at 30-day intervals, with joint manipulation occurring the day after each injection. The results from the study indicated that CCH significantly improved joint function and reduced contractures compared to placebo. (41) Specifically, 64% of joints treated with CCH achieved a contracture of 0 to 5 degrees, compared to only 6.8% in the placebo group. Furthermore Hurst et al. found, that CCH-treated joints

demonstrated a significant increase in range of motion, with an average improvement of 36.7 degrees, highlighting its potential to restore hand function effectively.

A more recent study by Rohit et al. (2019) investigated Clostridium Histolyticum collagenase (CCH) injections, marketed as Xiapex®. (42) The aim of this prospective observational study conducted in Austria from 2011 to 2017 was to evaluate the safety and efficacy of Xiapex® under real-life conditions. It involved 788 patients and showed that CCH injections are effective in reducing Dupuytren's Disease contracture with minimal and transient side effects. The most common side effect was skin rupture, which was estimated with 26%. (42) The study found that patient satisfaction and functional improvement were high and that the rate of surgeries required after treatment was low, reported at 2% within one year. However, according to the authors, the study has limitations, including potential missing follow-up data due to the non-mandatory reporting by physicians and patient dropouts. The maximum follow-up period of 1 year may also be insufficient for fully assessing the recurrence rate. Additionally, there might be a selection bias since physicians were not obligated to report all treated patients. In order to ensure the validation of the collected data, future research could increase the follow-up time frame to obtain more precise recurrence rates.

Radiotherapy

Radiotherapy is considered an alternative non-invasive treatment for early-stage Dupuytren's Disease that aims to prevent disease progression. (43) It uses ionizing radiation to target and potentially reduce the fibroblastic proliferation characteristic of Dupuytren's Disease. (44) Therapy is usually recommended for patients with mild to moderate symptoms in whom nodules and fascicles are present without significant contractures. (45) A study from Betza et al. looked at the long-term consequences of radiotherapy for early-stage Dupuytren's contracture and late toxicity over a median follow-up period of 13 years. (46) They found that radiotherapy was effective in preventing disease progression in many patients, especially in the early stages (N and N/I), with only minor late skin toxicity observed in some patients. Importantly, radiotherapy did not complicate subsequent surgical interventions for disease progression. This supports the idea that radiotherapy may be an appropriate treatment for early-stage Dupuytren's Disease, which relieves symptoms and stabilizes the disease without significant adverse effects.

Another review by Park and Lee (2017) highlights the radiobiological mechanisms and clinical application of low-dose radiotherapy for the treatment of non-malignant diseases, emphasizing its efficacy and safety, especially in elderly patients. (47) According to the research, low-dose

radiotherapy has an anti-inflammatory effect that is useful in the treatment of a wide range of diseases, from degenerative diseases such as osteoarthritis to hyperproliferative disorders such as Dupuytren's Disease. Despite concerns about the potential risks of radiation, evidence suggests that with modern radiotherapy techniques and precautions, the risk of secondary malignancies is minimal, especially in older patients. (47)

Extracorporeal shock wave therapy

Extracorporeal shock wave therapy (ESWT) has emerged as an innovative, non-invasive treatment option for Dupuytren's Disease. This therapy focuses on the delivery of shock waves to the affected areas and aims to relieve pain, improve function, and potentially slow the progression of the disease. (48) By targeting the fibrous tissue formations, ESWT is a promising alternative to traditional surgical and non-surgical treatments, offering patients a less invasive option that is associated with fewer risks and complications. (49)

A study by Aykut et al. investigated the potential of extracorporeal shock wave therapy in the treatment of Dupuytren's Disease, focusing in particular on early-stage palmar nodules. (50) The aim was to determine whether ESWT can alleviate symptoms, improve hand function, and delay the need for surgery. The study, which involved 23 patients, consisted of weekly ESWT sessions over a six-week period, with outcomes measured by VAS score, Quick-DASH questionnaire, MAYO wrist score, and grip strength. The results indicated significant improvements in function, suggesting that ESWT is a viable, non-invasive treatment option that can improve the quality of life of patients with Dupuytren's Disease and delay surgical intervention, especially in patients with severe comorbidities.

Further studies by Taheri et al. looked at the benefits of shockwave therapy for Dupuytren's Disease and showed a significant reduction in symptoms and improvement in hand function over 14 weeks. (51) According to the findings, ESWT represents a compelling non-surgical treatment alternative that may delay or reduce the need for invasive procedures. Through careful evaluation, the study highlights the effectiveness of shockwave therapy in improving grip strength and reducing finger contractures. It also advocates its inclusion in early treatment strategies for Dupuytren's Disease. However, the study that was conducted faces limitations, including a small sample size and a short follow-up period. These constraints may affect the generalizability of the findings and highlight the need for more extensive research with longer follow-ups to establish a definitive treatment protocol for ESWT in Dupuytren's Contracture.

VII. SURGICAL INTERVENTIONS

As the disease progresses, traditional treatments may no longer suffice, leading to the need for surgery to improve hand function and relieve symptoms. (52) Due to the complexities of Dupuytren's Disease, the intricate nature of hand anatomy, and the crucial importance of preserving functionality, choosing the right approach is vital. This section explores the range of options for treating Dupuytren's Disease, offering a look at various techniques, a comparison of their effectiveness, and insights into post-operative recovery and rehabilitation.

Percutaneous Needle Fasciotomy

Needle Aponeurotomy (NA), also known as Percutaneous Needle Fasciotomy (PNF), is a minimally invasive procedure utilized in the management of Dupuytren's Disease (DD). (15) According to an international review by Warwick et al. (2021), this technique is particularly appealing for its outpatient setting, minimal recovery time, and reduced need for extensive physical therapy post-procedure. (53) It is best suited for patients with less severe contractures or those who prioritize a quick return to daily activities. (53)The NA/PNF procedure involves the use of a small needle, typically a hypodermic needle, which is inserted through the skin into the fibrous cords, causing the contracture. (54) The surgeon then uses the needle to puncture and weaken these cords in multiple places. By manipulating the affected finger, the weakened cords can be broken, leading to an improvement in finger extension and hand function (see Figure 4). The procedure is usually performed under local anesthesia, and the patient is awake during the process. (55)

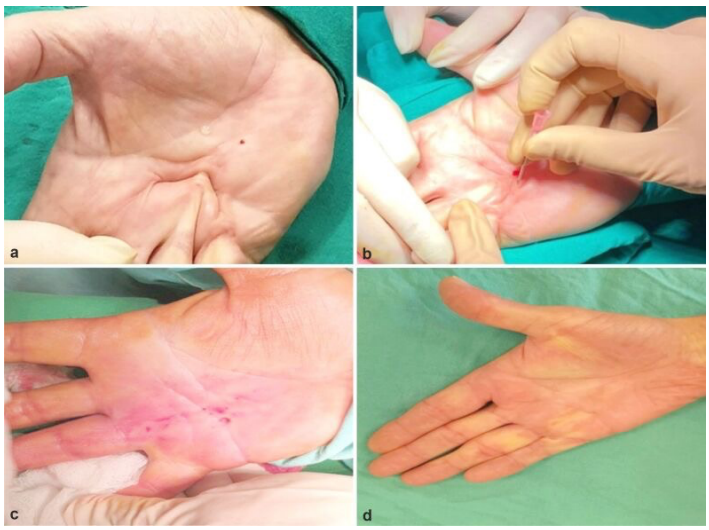

Figure 4: a) Preintervention, b) Intervention, c) Result, d) One year result; Trâmbiţaş, 2021 (5) CC BY-NC-SA 4.0

According to Warwick et al. (2021), NA/PNF is most effective for patients with primary contractures in the metacarpophalangeal (MCP) joints and less severe contractures in the proximal interphalangeal (PIP) joints. (53) Therefore, it might be an excellent option for elderly patients, those with comorbid conditions that make them poor candidates for more invasive surgeries, or individuals seeking treatment with a quick recovery. (56)

Needle Aponeurotomy offers several advantages. This procedure is distinctive for not requiring incisions, significantly reducing the risk of complications associated with traditional surgery, such as infection and issues with wound healing. This key advantage makes it a preferred choice for patients and surgeons aiming for a procedure with a safety profile. (57)

One of the most appealing aspects of Needle Aponeurotomy is the quick recovery time. Patients undergoing this procedure typically experience minimal downtime and are often able to resume their normal activities shortly after the procedure, making it highly convenient for those seeking minimal interruption to their daily lives. Additionally, this technique is performed under local anesthesia as an outpatient procedure, allowing patients to go home on the same day, further emphasizing its convenience and efficiency. (58)

The procedure's repeatability is another notable advantage. In cases where contractures recur or if the initial improvement is deemed insufficient, Needle Aponeurotomy can be performed again, providing flexibility and ongoing management options for patients with Dupuytren's Disease. (59)

Despite these benefits, Needle Aponeurotomy comes with limitations. Recurrence rates after the procedure are higher compared to more invasive surgical techniques, which may necessitate repeated interventions over time. (60) Studies have shown that NA/PNF can provide significant immediate improvement in finger extension and hand function. (61) The effectiveness of this technique may also be limited, particularly for severe contractures or those involving the proximal interphalangeal (PIP) joints, potentially making it a less suitable option for patients with advanced disease. (60) Moreover, there is a rare but present risk of nerve or tendon injury (e.g. deep common flexor tendon) due to the procedure's percutaneous nature. (62) While the incidence of such complications is low, it is a consideration that must be taken into account when deciding on the appropriateness of Needle Aponeurotomy for individual patients.

Post-operative care for NA/PNF is relatively straightforward, focusing on maintaining the improved finger extension achieved during the procedure. (63) Light hand therapy may be recommended to optimize hand function and prevent scar tissue formation. Patients are encouraged to resume normal activities as tolerated, which contributes to the procedure's appeal. (55)

Partial Fasciectomy

Partial fasciectomy remains one of the cornerstones of surgical treatment for Dupuytren's disease, specifically tailored for patients with moderate to severe contractures. (64) This procedure selectively removes diseased segments of the palmar fascia, specifically targeting fibrotic cords and nodules that cause deformities in finger flexion (see Figure 5). (65) By concentrating on these affected areas, partial fasciectomy not only alleviates contractures but also preserves as much healthy tissue as possible, maintaining the overall function and aesthetic of the hand as it can be observed on the right picture.

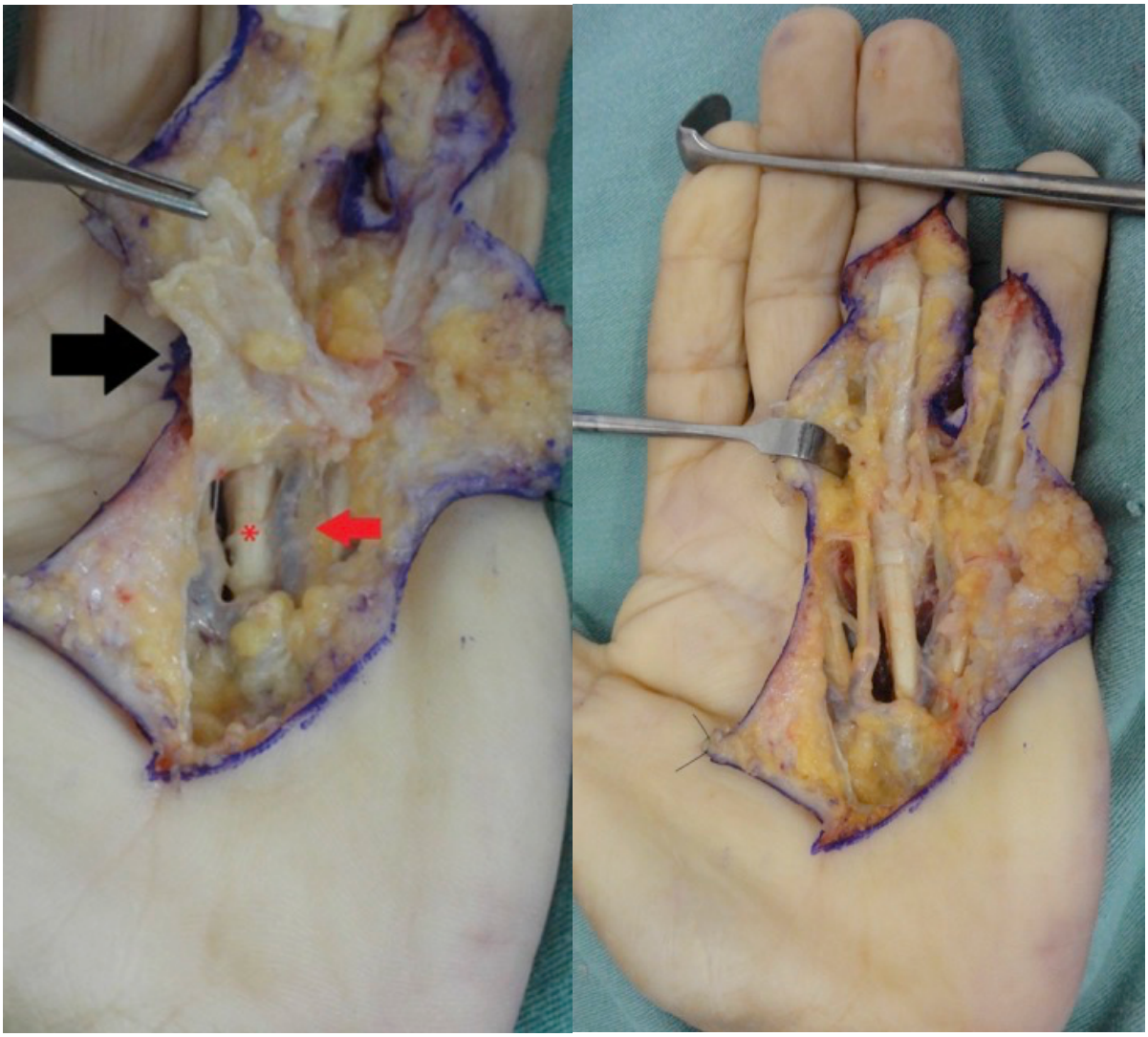

Figure 5: Partial Fasciectomy, left) Identification of the cord (black arrow), neurovascular bundle (red arrow) and flexor tendons (red cross); right) Excision of affected tissue; Ribak et al., 2013 (66) CC BY-NC-ND

Therefore, partial fasciectomy allows for a more focused treatment of Dupuytren's Disease, in comparison to total fasciectomy which has been popular during the first half of the 20th century. (67) (27) Patients undergoing partial fasciectomy often report significant improvements in hand function and quality of life. (68)

While recurrence of Dupuytren's Disease is a concern with any surgical intervention, Partial Fasciectomy can offer a lower recurrence rate in the specifically treated segments compared to less invasive methods. (69) By excising the fibrotic tissue, the procedure directly removes the source of the contracture, potentially leading to more durable results in the operated areas.

However, other studies suggested that despite the effectiveness of Partial Fasciectomy in treating specific areas of Dupuytren's Disease, the disease may recur in other parts of the hand or even in the same area. According to a randomized clinical trial by van Rijssen et al. (2012), the recurrence rate of segmental fasciectomy exceeded twenty percent. (61) Nevertheless, the recurrence rate of needle fasciotomy was estimated to be higher at 84.9 percent in a five-year interval after the intervention. (61) Another systematic review conducted by Chen et al. (2011) the estimated recurrence rate after partial fasciectomy for Dupuytren's contracture ranged from 12% to 39%, with the follow-up period varying from 1.5 to 7.3 years. (70) The study by Chen suggests, that this wide range highlights the variability in outcomes depending on factors such as surgical technique, severity of the disease at the time of surgery, and length of follow-up. Therefore, the risk of recurrence necessitates ongoing monitoring and, in some cases, additional treatment.

Partial fasciectomy, is effectively complemented by the open palm technique developed by McCash in 1964. (71) This technique is renowned for its low complication rate, making it a valuable method for treating advanced disease. During the procedure the affected tissue is removed by a tranverse incision, which is left open postoperatively as it is shown in Figure 6. (71) The open palm technique facilitates rapid healing and reduces the likelihood of complications such as infection, haematoma and skin necrosis. (72) According to a study conducted by Malta et al. in 2013, by leaving the surgical wound open, an allowance for a more natural skin contraction and granulation can be obtained, ultimately leading to better healing dynamics. (73) The results of Malta et al. display, that the wounds usually close within about 25 days and it has been shown to successfully correct deformities without restricting post-operative joint movement. In this study the reported deformity correction rate was 92%. However, the study was conducted with a relatively limited sample size of 12 patients, which may restrict the generalizability of the findings.

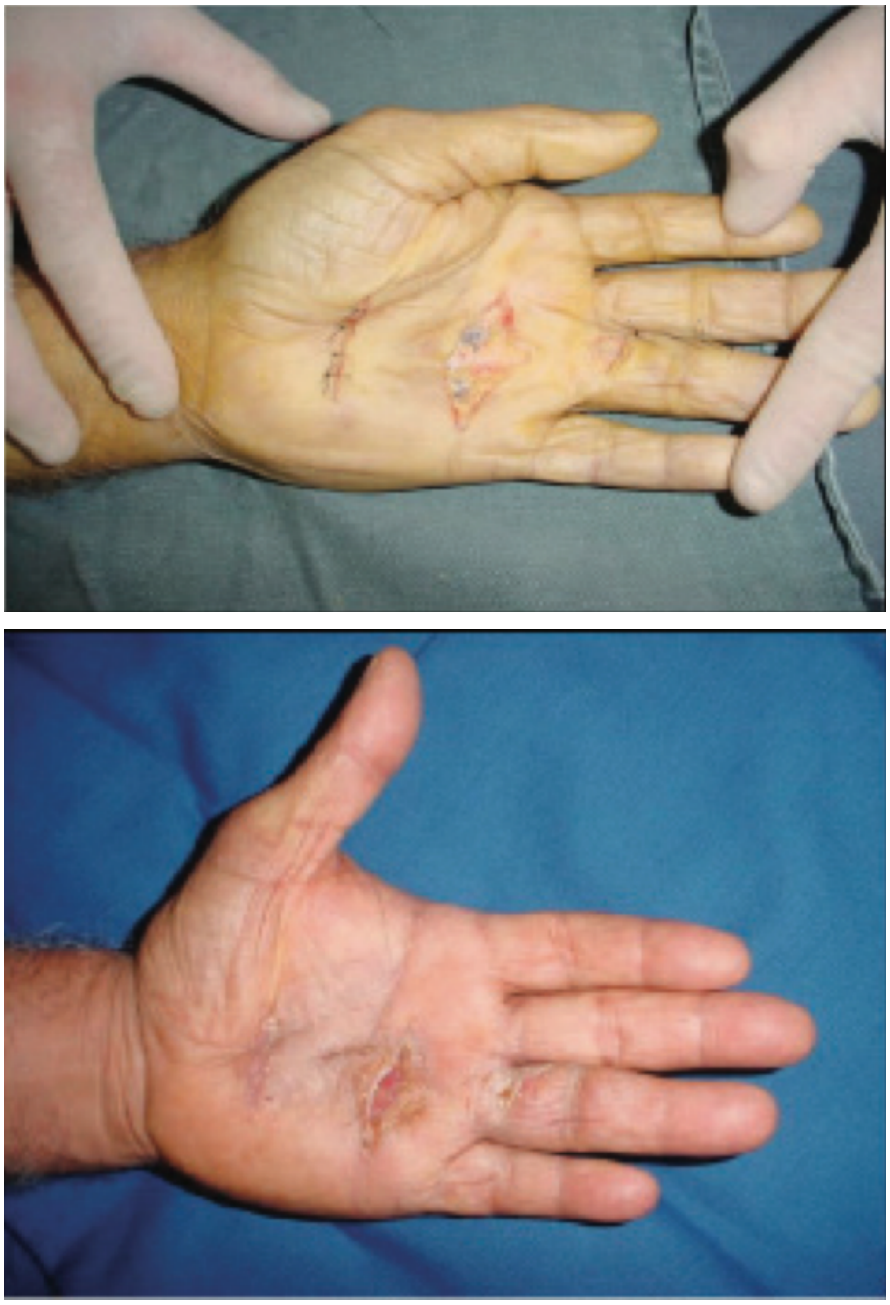

Figure 6: Open palm technique; above) perioperative view, with identifiaction of the longitudinal cord; below) 25 days after the operation; Malta et al., 2013 (73) CC BY-NC-ND

As mentioned before, one of the key benefits of Partial Fasciectomy is its focus on conserving unaffected palmar fascia and surrounding structures. This preservation of healthy tissue supports more satisfactory hand function post-surgery and may facilitate a smoother rehabilitation process. (74) Although recovery from Partial Fasciectomy may be longer than that of less invasive procedures, it is generally shorter than the recovery period following a Total Fasciectomy. Patients can often resume their normal activities and return to work within a few weeks, depending on the extent of the surgery and their individual healing process. (64)

As with any surgical procedure, Partial Fasciectomy carries potential risks, including infection, hematoma formation, nerve or tendon injury, and delayed wound healing. These complications can impact the overall recovery and outcome of the surgery. (75) Successful recovery from Partial Fasciectomy often requires a dedicated rehabilitation program to restore hand strength, flexibility, and function. (68) This process can be time-consuming and demands active participation from the patient to achieve optimal results.

Dermofasciectomy

Dermofasciectomy is a surgical treatment option for Dupuytren's Disease, particularly in cases with severe skin involvement or a high risk of recurrence. (76) First described by Hueston in 1962, the procedure involves the excision of the diseased palmar fascia along with the overlying skin, which is then replaced with a skin graft. (77) (78)

The surgical technique for dermofasciectomy includes the removal of the fibrotic cord along with the affected skin. (79) The resulting defect is covered with a skin graft, usually harvested from the forearm, groin, or antecubital fossa. This approach not only addresses the contracture by removing the diseased fascia but also reduces the likelihood of recurrence by replacing the skin, which may harbor disease-contributing fibroblasts. (79)

This procedure is beneficial for severe or recurrent cases where the skin is significantly involved, offering a more definitive treatment by addressing all diseased tissue. (80) The use of skin grafts can improve the quality and flexibility of the skin in the operated area, aiding in hand function and appearance. (79)

On the other hand, dermofasciectomy is a more complex procedure than fasciectomy alone, requiring skin grafting and, therefore, resulting in a longer recovery period. Patients may experience more significant post-operative pain and a longer rehabilitation process.

The success of dermofasciectomy heavily relies on the graft's take. Complications such as graft failure, infection, or scarring can impact the outcome and may necessitate additional surgical interventions. (79) (81)

VIII. COMPARATIVE ANALYSIS: SURGERY VS CONSERVATIVE TREATMENT

The comparative analysis between surgical and non-surgical treatment approaches for Dupuytren's Disease should include a comprehensive evaluation of their efficacy, advantages,

disadvantages and patient-centered outcomes. The following table summarizes the main results of the reviewed literature between conservative and surgical treatment methods.

Table 3 Surgical and non-surgical treatment approaches

Treatment Approach	*Efficacy*	*Benefits*	*Limitations*	*Recurrence Risk*
Physical Therapy & Splinting	Limited evidence	Non-invasive, may improve function	Unstandardized outcomes, variable effectiveness	Not applicable
CCH Injections	Effective in reducing contractures	Less invasive, fast recovery	Potential bias of studies, short follow-up	Low to moderate
Radiotherapy	Effective in early stages	Prevents progression, minimal toxicity	Concerns about radiation risks	Low
ESWT	Significant improvement in function	Non-invasive, no surgery required	Small sample sizes of studies, short follow-up	Unknown
PNF	Effective for less severe contractures	Fast recovery	Higher recurrence rates, limited for severe contractures	High
Partial Fasciectomy	Effective in improving hand function	Targeted treatment, moderate recovery time	Recurrence, potential complications	Moderate to high
Dermofasciectomy	Reduces risk of recurrence	Addresses severe/recurrent cases	Surgically more complex, longer recovery, graft-related complications	Low

The choice of the listed treatment approaches is influenced by several factors. While conservative treatment strategies prioritize symptom management, improvement of hand function, and delaying disease progression, surgical treatments become necessary as Dupuytren's Disease progresses, with the goal of improving hand function and relieving symptoms. Conservative approaches are particularly important in the early stages of the disease or in patients for whom surgery is not indicated or desirable. If surgical intervention is indicated, choosing the right surgical approach is critical, considering the intricate nature of hand anatomy and the importance of preserving functionality.

Another part that drives decision-making in practice is the cost-effectiveness of treatment approaches. (82) It allows for an assessment of the relative value of different treatment strategies, considering their costs and outcomes. In a study by Alfred Yoon et al. (2020) in Michigan, an economic evaluation of different treatment methods was undertaken. (83) Based on the study results provided, the most cost-effective treatment for recurrent Dupuytren's contracture varies significantly depending on the severity of the contracture and the joint involved. According to Yoon et al., for recurrent severe metacarpophalangeal joint contractures, limited fasciectomy emerges as the most cost-effective option compared to percutaneous needle aponeurotomy. The study found, on the other hand, that for low-severity MCP Joint and proximal interphalangeal joint contractures, PNA stands out as the only cost-effective treatment. According to Yoon et al., its minimal invasiveness, lower cost, and quick recovery make it an ideal first-line intervention for less severe contractures.

In conclusion, the comparison of treatment methods for Dupuytren's Disease showcases a range of choices, each having its advantages, drawbacks, and factors to consider. Non-invasive treatments present options for early-stage conditions or as supplementary treatments to surgery, focusing on managing symptoms and enhancing functionality with minimal risks. Surgical procedures, though more invasive, offer potentially longer-lasting solutions for advanced conditions considering aspects such as recovery time, risk of complications, and chances of recurrence. Ultimately, the treatment decision should be tailored to the individual by considering the disease stage, patient preferences, and overall well-being to ensure that the chosen approach is in line with their needs.

IX. CONCLUSIONS

This literature review on Dupuytren's Disease has synthesized key insights into its etiology, progression, and management, shedding light on the complexity of the condition and its significant impact on patient lives. The central role of myofibroblasts in the pathogenesis of the disease, the genetic basis, and the links with systemic diseases such as type 2 diabetes mellitus, and lifestyle factors such as alcohol consumption were emphasized. The treatment of Dupuytren's disease is constantly evolving, integrating new research and clinical practices to improve patient outcomes. Here are the cornerstone conclusions drawn from the comprehensive review:

1. **Multifactorial aetiology**: Dupuytren's disease manifests itself as a complex interaction of genetic predispositions and environmental exposures, and it is important to tailor treatment to individual risk factors.
2. **The importance of early diagnosis**: early diagnosis and intervention have a major impact on treatment outcomes, and it is therefore essential to inform and regularly monitor those at risk.
3. **Advancements in Non-Surgical Treatments**: Innovations in non-invasive treatments, in particular the use of Clostridium histolyticum collagenase, are showing promising results and point to the need to move towards less invasive treatment strategies where appropriate.
4. **Effectiveness of surgery**: Surgical interventions, especially partial fasciectomy, remain the cornerstone in advanced stages of Dupuytren's Disease, as they are effective in resolving contractures and reducing recurrences. However, the choice between surgical options should consider the potential complications and recovery time.

Strategic Recommendations for Clinical Practice:

1) **Treatment Modalities Tailored to Disease Severity**:
   - In **early and mild cases**, non-surgical measures such as Clostridium histolyticum collagenase injections or radiotherapy are recommended because they are minimally invasive and effectively slow the progression of the disease.
   - **Moderate cases**: techniques such as needle aponeurotomy can strike a balance between invasiveness and efficacy.
   - **Advanced cases**: Partial fasciectomy is recommended to remove severe contractures and to reduce the risk of recurrence in view of its greater effectiveness in restoring hand function.
2) **Treatment Modality Selection Based on Patient Profile**:
   - **Active individuals or workers**: minimally invasive treatments, such as collagenase injections, are preferred for faster recovery, allowing a quicker return to daily activities.
   - **Elderly people or patients with comorbidities**: less aggressive surgical treatment or conservative treatment may be appropriate to avoid the risks associated with major surgery.
   - **Patients with recurrent disease**: For patients with recurrent disease, more invasive surgical treatments, such as partial fasciectomy, may be considered, which provide a more permanent solution despite a higher risk of complications.

X. FUTURE DIRECTIONS

As the understanding of Dupuytren's Disease continues to advance, it is increasingly important to focus on new areas of research that can further improve treatments and patient outcomes. Looking to the future, several key areas of research have been identified that promise to substantially improve the treatment of this complex disease:

- Genetic and molecular research: further exploration of the genetic factors and molecular mechanisms underlying Dupuytren's Disease could lead to the development of targeted therapies that may offer non-surgical options for treating the disease.
- Long-term studies: There is a need for long-term follow-up studies to better understand the natural history of the disease and the long-term efficacy and safety of both conservative and surgical treatments.
- Preventive strategies: Research into the impact of modifiable risk factors, such as lifestyle changes, on the progression of Dupuytren's Disease could provide information on prevention strategies that could reduce the incidence or severity of the disease.
- Patient-reported outcomes: Future studies should incorporate patient-reported outcomes to assess the impact of Dupuytren's Disease and its treatments on quality of life to contribute to patient-centered care.
- Technological advances: Research into new technologies, including minimally invasive surgical techniques and novel conservative treatments, could lead to better outcomes for patients with Dupuytren's Disease.

By addressing these areas, future research can provide deeper insights into Dupuytren's Disease, leading to more effective and personalized treatment options. As we conclude this literature review, it is clear that embracing these future directions will be crucial for continuing to improve the lives of those affected by Dupuytren's Disease. The ongoing pursuit of knowledge and innovation in the management of Dupuytren's Disease promises to transform our approach to this complex condition, offering hope for more effective and personalized care in the future.

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