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Fibroblast Phenotypic Plasticity in Coexistent Dupuytren Disease and Localized Scleroderma

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Abstract

Dupuytren's disease is a condition in which the palmar fascia undergoes fibro proliferation, ultimately leading to a flexion contraction of the fingers. The pathophysiology of Dupuytren's disease includes complex fibrotic processes, with myofibroblasts playing a key role in its underlying mechanism. The phenotypes of fibroblasts vary between different pathologies. In Dupuytren's disease, fibroblasts often migrate slower compared to other fibroblasts. The phenotype of fibroblasts in Dupuytren's disease can be related to the phenotypes seen in fibroblasts involved in scleroderma. Scleroderma can be categorized based on presentation, with diffuse scleroderma involving various internal systems and localized scleroderma, also known as morphea, being a skin-limited disorder. This literature review will discuss localized scleroderma only. The pathophysiology of localized scleroderma involves inflammatory processes leading to abnormal fibrosis of the skin, therefore leading to potential disfigurement of the body. Fibroblasts play a significant role in this process, similarly to Dupuytren's disease. This literature review will uncover parallels in the phenotypes of fibroblasts and fibrotic processes in both Dupuytren's disease and localized scleroderma.

1. Introduction

Dupuytren's disease is a chronic, progressive disorder affecting the hand. Referred to as the "Viking Disease," Dupuytren's contractures are more commonly seen in people of Northern European descent, mainly due to higher prevalence of specific genetic risk variants in these populations [1]. First identified by Baron Guillaume Dupuytren in 1831, this disease affects the palmar fascia of the hand, a dense connective tissue network crucial to maintenance and support of the palmar blood vessels, nerves, and tendons [1, 2]. Composed of three distinct layers, the superficial, or pretendinous layer, responsible for providing overall stability to the palm, is the most affected with fibro proliferative changes causing progressive flexion contractures of the fingers, most commonly the ring and small digits [3]. While the majority of cases are painless, progressive contractures can significantly impair hand functions, causing difficulties with activities of daily living [1].

The pathophysiology of the uncontrolled palmar fascia growth typical of Dupuytren's disease is complex and multifactorial, being described in three phases: proliferative phase, involutional phase, and residual phase [4]. The proliferative phase starts with an increase in the number of fibroblasts within the palmar fascia, causing the development of nodules without contractures in the hand. The progressive nature of the disease causes fibroblasts to differentiate into

myofibroblasts, which are specialized cells that play a key role in tissue repair and mediating wound contractures. With increasing deposition of mainly type III collagen, the proliferative phase transitions into the involutional phase, characterized by the development of finger flexion contractures [5]. In this phase, the myofibroblasts start to contract and align along the length of the fascia divided into several pretendinous bands attached to skin just behind the metacarpophalangeal (MCP) joint [5]. Contraction of these pretendinous bands subsequently leads to the characteristic contractures at the MCP joints. Finally, cord development and joint changes are seen in the residual phase of the disease, where permanent finger deformities can result without intervention [6].

Scleroderma is an autoimmune, rare connective tissue disease also characterized by hardening and fibrosis of the skin. Dating as far back as 400 BC, scleroderma is characterized by widespread microvascular damage and excessive collagen deposition in the skin [7]. Three subgroups of scleroderma exist: diffuse scleroderma, limited scleroderma, and localized scleroderma [7]. This literature review will focus on localized scleroderma due to its localized dermatologic manifestations. Localized scleroderma typically develops between the ages of 30 to 50 and is more prevalent in African-American women [8]. It is usually self-limited and clinically marked with antinuclear antibodies (ANA). Also referred to as morphea, many subtypes exist with plaque morphea, which are typically described as a well-circumscribed, round, hard, shiny skin [9]. Like Dupuytren's contracture, localized scleroderma also progresses through distinct stages. In the inflammatory stage, symptoms typically begin with erythema, swelling, and occasional itchiness, indicating active inflammation. The sclerotic phase follows, where the affected skin starts to thicken and harden, manifesting the classic signs seen in scleroderma. Localized scleroderma progressions end with the atrophic phase, where the thickened skin starts to atrophy, causing thinning of the skin with possible muscle loss [9, 10].

Similarly to Dupuytren’s disease, the pathophysiology of localized scleroderma involves progressive fibrosis of the skin. However, unlike Dupuytren’s, vascular injury precedes fibrosis in localized scleroderma. Early endothelial damage, mainly in the arterioles, triggers inflammatory changes and recruitment of immune cells, which then release autoantibodies, chemokines, and cytokines. These factors stimulate resident fibroblasts to differentiate into myofibroblasts, similarly to Dupuytren's, leading to progressive extracellular matrix deposition of different collagen types (mainly type I collagen), proteoglycans, and elastic fibers like fibrillin, resulting in the classic manifestation of tissue stiffening [11, 12].

In addition to a brief overview of the pathophysiology of Dupuytren’s and localized scleroderma, understanding the extracellular matrix (ECM), fibrosis, and fibroblast plasticity is also essential to further highlight commonalities between the two diseases. As mentioned previously, ECM is produced in nearly all human cells and is composed of proteoglycans – fibrous proteins like collagen and elastin – and adhesion molecules like fibronectin, which all play a crucial role in maintaining the structural integrity of resident cells [13]. Without proper function of the ECM, processes like development, morphogenesis, and wound repair would be significantly affected with too little or too much accumulation of ECM resulting in connective tissue disorders and organ fibrosis respectively [13]. While fibrosis is needed for wound repair and healing, excess fibrosis can result in differentiation of fibroblasts into myofibroblasts, using this plasticity to progress Dupuytren’s disease and localized scleroderma [14-16].

Myofibroblasts (CD82) are fibroblasts that express alpha-smooth muscle actin induced by transforming growth factor - beta (TGF-β), leading to its highly contractile nature, and contributing to its classic phenotypes of cords and nodules [17, 18] While these can occur at the same time in the same patient, many differences at the molecular level exist between these phenotypes. When looking at nodules, they typically have higher levels of alpha-smooth muscle actin, CD68 positive cells (marker for macrophages), collagen type I and V, fibronectin, and elastin compared to cords [18]. No differences were observed in CD31 positive cells (marker for blood vessels) or collagen types III and IV [19]. In addition to differences between the two Dupuytren’s phenotypes, many factors are involved in driving inflammation to promote fibrosis progression. Specifically, ICAM1+IL6 and CD34+ are fibroblast subtypes that express high levels of chemokines essential for driving fibrosis [17].

Like Dupuytren’s disease, localized scleroderma involves the activation of myofibroblasts,

primarily driven by TGF-β signaling. However, localized scleroderma exhibits a broader range of fibroblast phenotypes with distinct functional roles in fibrosis [20]. In addition to TGF-β, localized scleroderma also engages interferon (IFN) signaling pathways, contributing to its complex inflammatory profile [21]. Notable fibroblast subsets include SFRP2+ fibroblasts, which are small, elongated cells located between collagen bundles and play a key role in myofibroblast differentiation [22, 24]. Other relevant markers include CXCL2 (a chemoattractant), IRF1 (a transcription factor involved in immune activation), and CCL19, a chemokine essential for leukocyte recruitment and sustaining a proinflammatory microenvironment [24-28].

While many clinical and histological differences exist between these two diseases, Dupuytren's and localized scleroderma start to significantly overlap when discussing fibroblast phenotype plasticity and remodeling. Therefore, a deeper understanding of these overlapping pathways will prove to be useful in enhancing our ability to diagnose, manage, and treat these diseases.

2. Methods

A systematic search for publications was conducted by eight independent reviewers using two electronic databases: PubMed and Google Scholar. The search strategy combined keywords and MeSH terms related to "Dupuytren's Contracture," "Limited Scleroderma," "Fibroblast Plasticity," "Myofibroblasts," and "Morphea." Only studies evaluating fibroblast plasticity in Dupuytren's disease and limited scleroderma were included. Studies that focused on fibroblast plasticity in other fibroblast associated disorders were excluded. The articles selected for this paper were published between December, 1989 and February, 2025. The last database search for articles was conducted on July 9, 2025. No meta-analysis was performed.

3. Clinical Implications And Outcomes

3.1. Clinical Presentation

Dupuytren's disease (DD) and localized scleroderma (morphea) are two distinct fibrotic disorders with different clinical presentations. While they are unrelated in origin and rarely occur together in the same individual, they share core pathologic features, such as fibroblast activation and extracellular matrix accumulation, which ultimately lead to progressive tissue thickening and loss of normal function. These similarities may help explain why both conditions are often studied in the context of broader fibrotic mechanisms, despite their clinical and anatomical differences.

DD is most often seen in middle-aged to older adults, which usually presents as a gradual thickening of the palmar fascia [29]. Over time, this fibrous tissue develops into palpable cords that pull the fingers, especially the ring and little fingers, into a flexed position at the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints [29]. The resulting contracture can interfere with basic tasks like gripping, typing, which can affect an individual's ability to work and daily independence [29]. Prevalence is highest in men of Northern European ancestry [29]. It is more common in those with a history of manual labor, suggesting that biomechanical stress may contribute to disease progression in genetically susceptible individuals [29]. This demographic association has led researchers to explore how both environmental and constitutional factors contribute to the onset and severity of disease, offering insights into the interaction between tissue-specific stress and systemic predisposition.

Histologically, DD is characterized by dense aggregates of myofibroblasts and a shift in collagen composition, with a higher ratio of type III to type I collagen [30]. This pattern is more typical of wound healing and fibrotic scarring than of normal fascia, and it may explain the contractile behavior of the tissue [30]. These findings reinforce the view of DD as a localized fibro proliferative condition, where chronic remodeling of the extracellular matrix takes place even in the absence of obvious ongoing inflammation. Understanding these features is key to differentiating DD from other causes of hand dysfunction, especially in atypical presentations.

In contrast, localized scleroderma, also known as morphea, is a chronic fibrosing skin condition that falls within the spectrum of autoimmune connective tissue diseases [31]. Unlike systemic sclerosis, which can involve internal organs and carries a risk of life-threatening complications, morphea is confined to the skin and underlying soft tissues [31]. It most commonly presents as circumscribed, hardened plaques, but may also appear in linear or generalized forms. Linear morphea, particularly when it affects the limbs or face, can extend deeply into subcutaneous fat, fascia, and even muscle or bone [31]. These deeper forms are more often seen in children and can result in long-term functional and cosmetic impairment if not identified early [31]. Despite

its limited distribution, the burden of morphea can be substantial. Inflammatory patches may evolve into firm, discolored areas with reduced elasticity, sometimes resembling burn scars or post-traumatic changes [31]. This variability in presentation contributes to delays in diagnosis, especially when early lesions are subtle. Unlike DD, which is often diagnosed clinically based on characteristic hand involvement, morphea frequently requires biopsy to confirm the diagnosis, and to rule out other conditions. The absence of systemic symptoms may also lead to underestimation of disease impact by both patients and clinicians.

The terminology used to describe morphea can further complicate the clinical picture. Because the word "scleroderma" is associated with systemic disease, patients may have misunderstandings about their diagnosis [31]. This confusion may lead to unnecessary testing or referrals [31]. Clinicians increasingly favor the use of "localized scleroderma" or simply "morphea" to distinguish it from systemic sclerosis, but inconsistencies in language persist in both medical records and patient education materials [31]. Clear, consistent terminology is essential for diagnostic accuracy and appropriate disease management.

While DD and morphea differ significantly in clinical scope and presentation, both involve a fibrotic process driven by activated fibroblasts and abnormal immune signaling. Recognizing the characteristic patterns, hand contractures in DD versus inflammatory skin changes in morphea, can guide early diagnosis and reduce misclassification. Understanding their differences, as well as their shared features, provides a broader perspective on how localized fibrotic diseases develop and progress across different tissues.

3.2. Epidemiology of Localized Scleroderma

Understanding of the epidemiology of localized scleroderma, particularly morphea, has evolved significantly over the past few decades. In the late 1980s, data were sparse and fragmented, with most knowledge coming from case reports and small studies rather than population-based research [32]. Schachter emphasized the lack of comprehensive prevalence data at that time, highlighting just how little was known [32]. One of the earliest and most frequently cited estimates, drawn from the work of Professor Alan Silman, a leading British epidemiologist specializing in rheumatic diseases, suggested that morphea occurred at a rate of 2 per million males and 4.7 per million females, a strikingly low figure that emphasized its rarity [33]. In comparison, systemic sclerosis was found to be almost nine times more prevalent and showed an even more pronounced female predominance [33]. Early reports also suggested differences in subtype distribution based on age: linear scleroderma being more common in children and plaque-type lesions more often seen in adults [33]. Subtypes, such as subcutaneous or guttate morphea, were reported to occur equally across age groups [33]. These patterns hinted at potential differences in immune response or developmental susceptibility, though those theories remain under investigation [33]. Importantly, many of these early estimates were likely underrepresented, shaped by diagnostic inconsistencies, lack of standardized criteria, and limited surveillance systems. While such limitations may have affected prevalence estimates for multiple diseases, it is unclear whether morphea was disproportionately underreported compared to systemic sclerosis. Much of the data relied on dermatologist reporting, which may have skewed subtype representation and failed to capture less obvious or early cases. This early historical perspective highlights how much understanding of the disease has changed and why modern, large-scale studies are critical to more accurately define disease burden and outcomes.

A turning point in morphea epidemiology came in 1997 with a study by Peterson et al., who used data from the Rochester Epidemiology Project to follow morphea cases in Olmsted County, Minnesota over a 33-year period [34]. They identified 82 cases, most of them in women, and calculated an age- and sex-adjusted incidence rate of 2.7 per 100,000 people [34]. Interestingly, incidence appeared to rise over time by approximately 3.6% per year, possibly reflecting better recognition and diagnosis [34]. By age 80, estimated prevalence reached roughly 2 per 1,000 [34]. Most patients showed improvement or softening of their lesions within a few years, though disease duration varied by subtype [34]. Plaque-type morphea tended to resolve faster, while deeper forms – particularly linear and deep morphea – were associated with longer disease duration, and a greater risk of complications like joint contractures or synovitis [34]. No cases progressed to systemic sclerosis, and internal organ involvement was not observed [34]. Survival rates were similar to those of the general population, helping reinforce the idea that

morphea is a distinct clinical entity, separate from systemic disease [34]. Overall, the study painted a more complex and nuanced picture of morphea, one that emphasized its heterogeneity and challenged the assumption that it was a rare, self-limited condition.

More recent work has added greater depth to our understanding of localized scleroderma. In 2024, Keum et al. published the most comprehensive epidemiologic analysis to date, using two massive national health databases to reassess incidence and prevalence across the United States [35]. Drawing from the TriNetX Collaborative Network and IBM MarketScan, which together included over 28 million patients, the study found a much higher incidence of morphea than previously reported: about 1.49 per 10,000 in TriNetX and 1.37 per 10,000 in MarketScan for patients under 65 [35]. These findings suggest that morphea is nearly four times more common than earlier estimates indicated. The study also confirmed a strong female predominance and noted that incidence increases steadily with age [35]. This observation contrasts with earlier findings from Peterson's cohort, which had not reported age-related trends [35]. This discrepancy may reflect evolving diagnostic practices or even shifts in risk factors over time, such as changes in occupational exposures among women, rather than a definitive error in earlier data. One important difference in methodology may explain this discrepancy: Peterson counted all individuals ever diagnosed with morphea by age 80, whereas Keum's group focused on patients with active disease. As a result, their prevalence numbers appeared lower, but likely reflect a more accurate snapshot of current clinical burden. Perhaps most significantly, their analysis reinforces that morphea is still under recognized and often underestimated in clinical practice. A condition once thought to be rare is now emerging as more common, with important implications for diagnosis, disease monitoring, and long-term management.

Expanding this perspective globally, a recent single-center study from India by Talluru et al. offers insight into morphea's clinical and epidemiologic features in a non-Western population. The study followed 136 patients, finding a strong female predominance (68%) and a mean age of onset around 21 years [36]. Linear morphea was the most frequently observed subtype, especially in children, with the extremities being the most commonly affected sites [36]. Although the cohort was composed entirely of Indian patients, the patterns mirrored those seen in Western populations, suggesting that morphea shares a similar clinical phenotype across diverse racial and geographic backgrounds [36]. The authors also emphasized the importance of early diagnosis and long-term follow-up, especially in pediatric patients, given the potential for lasting disability in deeper or more extensive forms [36]. This study adds to the growing body of evidence that morphea is not only more prevalent than once thought, but also clinically significant in regions beyond North America and Europe. It supports the need for continued global surveillance and increased awareness among dermatologists, rheumatologists, and other clinicians.

3.3. Epidemiology of Dupuytren's Disease

Epidemiologic studies consistently show that Dupuytren's disease (DD) primarily affects older white men, especially those of Northern European descent [37]. Ross described this pattern in one of the most cited reviews of the condition, noting that in some Scandinavian populations, up to 30 percent of men over age 60 show signs of the disease [37]. While the condition is far less common in Black, Asian, and Hispanic populations, the reasons behind these racial disparities remain uncertain [37]. What is clear, however, is that both age and sex are strong influencing factors: men tend to develop symptoms earlier, often in their 50s or 60s, while women usually present about a decade or two later, and with milder forms [37]. Bilateral involvement occurs in nearly half of all cases and often coexists with other fibro proliferative disorders, such as plantar fibromatosis or Peyronie's disease [37]. Genetics seem to play a key role, but early studies also pointed to environmental or lifestyle factors, such as manual labor, alcohol use, diabetes, epilepsy, and smoking, with mixed evidence for these associations at the time [37]. More long-term research is necessary, especially to better understand why DD behaves differently across demographic groups.

More recent work by Kozanoğlu et al. revisited these questions, focusing on recurrence and disease profile in a modern surgical cohort [38]. In their study of 69 patients undergoing treatment for DD, nearly 90 percent were men, with an average age of 68 at the time of surgery [38]. Most patients had unilateral disease with symptom duration before surgery averaging nine years, reflecting the gradual, progressive nature of Dupuytren's [38]. Interestingly, none of the

patients reported a family history of the disease [38]. Recurrence occurred in about 10 percent of cases [38]. First ray involvement, meaning the thumb, stood out as a statistically significant risk factor for recurrence, while bilateral disease showed a possible trend, but did not reach significance [38]. The team also looked at common risk factors like smoking, alcohol use, diabetes, and occupational strain, but none showed a consistent association with recurrence in this relatively small sample [38]. Notably, metacarpophalangeal (MCP) joint contractures tended to be less severe during recurrence, but interphalangeal (IP) joint stiffness persisted, which reinforces the need for ongoing follow-up even after successful treatment [38].

Although both DD and morphea fall under the broader category of localized fibrosing disorders, their epidemiologic patterns diverge significantly. Dupuytren's disproportionately affects older white men in Western countries and often has deep, culturally embedded recognition, particularly in surgical fields. In contrast, morphea is more frequently seen in younger women and remains under-recognized despite being more prevalent than older estimates suggest. Still, both conditions share some common ground: they are chronic, slow to be diagnosed, and can lead to long-term disability if not properly managed. This overlap in clinical trajectory, despite different demographic footprints, underscores the importance of improving early recognition and awareness across medical specialties.

3.4. Similarities/differences in fibroblast phenotypes/mechanisms/fibrogenic pathways between Dupuytren's Disease and Localized Scleroderma

3.4.1. Myofibroblast activation

In both Dupuytren's disease (DD) and morphea, fibroblasts transform into myofibroblasts that express α-smooth muscle actin (α-SMA), a key protein that drives tissue contraction and fibrosis in both conditions [39]. In DC, these myofibroblasts appear to sustain their activated state over time, continuing to produce α-SMA and other profibrotic signals even when removed from the fibrotic environment. Experimental studies have shown that fibroblasts from Dupuytren's nodules continue to synthesize α-SMA when implanted into healthy tissue, suggesting that their contractile behavior is not easily reversed [39]. These cells also demonstrate a higher expression of type I collagen and α-SMA mRNA compared to fibroblasts from normal palmar fascia, confirming their enhanced fibrogenic potential [39]. The persistence of this activated phenotype seems to result from autocrine signaling, where fibroblasts secrete their own cytokines, reinforcing their transition into myofibroblasts and promoting further cytokine production and proliferation [39]. Although the precise inhibitory signals that could reverse this process are still unclear, these findings highlight the self-sustaining nature of myofibroblast activation in DD, and support the idea that targeting this feedback loop could be key to halting disease progression.

Morphea exhibits similar mechanisms, with fibroblasts undergoing transformation into myofibroblasts in response to injury and sustained inflammatory signals [40]. This process is driven by a combination of cytokines, particularly IL-1, IL-6, and TGF-β, which promote fibroblast proliferation and α-SMA expression [40]. Normally, myofibroblasts deactivate once healing is complete, but in morphea, activated cells persist in the skin [40]. The result is continuous collagen production and matrix remodeling, leading to thickened plaques and dermal fibrosis [40]. Like in DD, these changes are fueled by a local environment rich in profibrotic signals, which prevents proper resolution of the wound healing response [40]. Understanding how this deregulation unfolds over time in morphea could help clarify why certain patients progress to deeper, more disabling forms of the disease while others remain limited to superficial plaques.

3.4.2. TGF-β pathway activation

In Dupuytren's disease (DD), the TGF-β signaling pathway plays a central role in promoting fibrosis through both Smad-dependent and Smad-independent mechanisms. TGF-β signals through type I and type II receptors, activating downstream effectors such as Smad2/3 and the ERK1/2 MAP kinase pathway [41]. Fibroblasts isolated from Dupuytren's tissue express elevated levels of TGF-β compared to controls, along with increased phosphorylation of Smad proteins and ERK1/2, both of which contribute to their enhanced proliferation and contractile behavior [41]. These signals drive the upregulation of key extracellular matrix components, including type I collagen and fibronectin, and also stimulate the expression of connective tissue growth factor (CTGF) and platelet-derived growth factor (PDGF), further amplifying the fibrotic response [41]. Importantly, pharmacologic inhibition of the

TGF-β receptor with SB-431542, or of ERK1/2 with MAP kinase inhibitors, significantly reduces contractility and growth in Dupuytren's fibroblasts [41]. The involvement of multiple downstream pathways shows that Dupuytren's fibroblasts rely on more than one route to maintain their fibrotic behavior. This kind of redundancy may help explain why fibrosis in DD continues to progress, even when external triggers are no longer present. A similar pattern is seen in morphea, where TGF-β signaling also drives collagen production and skin thickening through overlapping molecular routes. These comparable signaling programs suggest that DD and morphea may share a common fibrotic blueprint, despite affecting different tissues.

In morphea, the TGF-β signaling pathway plays a similarly critical role in driving fibrosis through both immune-mediated and stromal cell interactions [42]. TGF-β is produced by a range of activated cells, including Th_{17} and Th_{22} lymphocytes, keratinocytes, and damaged endothelial cells, and acts as a central mediator of fibroblast activation and matrix production [42]. Once released, TGF-β interacts with other profibrotic factors, such as PDGF, CTGF, and FGF, to promote fibroblast proliferation and their transition into myofibroblasts [42]. This response is further amplified through toll-like receptor 4 (TLR4) signaling, which enhances TGF-β activity, and reinforces the fibrotic loop [42]. In addition, cross-talk between keratinocytes and fibroblasts through developmental pathways like Wnt, Hedgehog, and Notch contributes to sustained fibroblast activation [42]. Together, these overlapping mechanisms create a self-perpetuating fibrotic environment in the skin, mirroring the multifaceted TGF-β-driven signaling observed in DD. This reinforces the idea that fibrosis may not simply be the result of one pathway being overactive, but rather the outcome of several interconnected signals failing to resolve in a controlled manner.

TGF-β plays a central role in both conditions, despite their different clinical presentations, which suggests that tissue-specific outcomes may depend less on the signal itself and more on how local cells respond to the biochemical signals. This raises important questions about whether cell type, tissue structure, or local immune context shapes the trajectory of fibrosis once TGF-β is activated. Understanding these context specific differences may be key to explaining why some fibrotic diseases remain localized while others progress systemically. This overlap highlights how a single signaling molecule can produce distinct disease outcomes depending on the cellular environment and tissue context, and invites deeper investigation into how shared pathways are modulated in tissue-specific ways.

3.4.3. Excessive Extracellular Matrix and Collagen Deposition

In Dupuytren's disease (DD), excess collagen deposition is a defining feature of the fibrotic tissue, especially within the palmar nodules [43]. While type I collagen is normally the dominant form in healthy fascia, Dupuytren's tissue shows an increase in total collagen, with a higher proportion of type III collagen relative to type I [43]. This imbalance is thought to result not only from increased synthesis but also from reduced degradation, particularly due to decreased expression of key collagenase genes [43]. For example, MMP1 and MMP3, which are responsible for breaking down interstitial collagens, are down regulated in Dupuytren's fibroblasts [43]. Similarly, MMP16, which activates MMP2, a protease that targets type III collagen, is also expressed at lower levels [43]. Together, these changes lead to the accumulation of collagen within the extracellular matrix, and contribute to increased tissue stiffness and contracture [43]. The upregulation of several other collagen genes in Dupuytren's fibroblasts further supports a shift toward a more fibrotic transcriptional profile [43]. This combination of enhanced collagen production and impaired breakdown highlights how ECM remodeling becomes imbalanced in DD, reinforcing a cycle of persistent fibrosis. It also raises important questions about whether similar imbalances are responsible for collagen buildup in other localized fibrotic conditions like morphea, where matrix turnover is also disrupted.

In morphea, the overproduction of collagen and accumulation of extracellular matrix (ECM) are central to the thickening and hardening of affected skin [44]. Although the initial trigger remains unclear, factors like trauma, infections, or radiation are thought to cause microvascular damage, setting off a cascade of inflammatory responses [44]. These sources can lead to the release of adhesion molecules like VCAM-1 and ICAM-1, which promote T-cell activation and the secretion of profibrotic cytokines, including TGF-β, PDGF, CTGF, and interleukins 4, 6, and 8 [44]. These signals stimulate fibroblasts to increase collagen synthesis while also reducing the expression of matrix metalloproteinases (MMPs), the enzymes responsible for breaking

down collagen [44]. As a result, collagen accumulates in the dermis, disrupting normal skin architecture and contributing to plaque formation and stiffness [44]. This imbalance between production and degradation reflects a breakdown in the body's ability to regulate ECM homeostasis. It also raises the possibility that, as in DD, morphea may involve not just fibroblast over activity, but a failure in the clearance mechanisms that would normally resolve fibrosis once healing is complete.

3.5. Treatment

Treatment for Dupuytren's disease (DD) has traditionally centered on surgical approaches, particularly fasciectomy procedures that physically remove the fibrotic tissue [45]. While surgery can improve hand function in the short-term, it often comes with downsides, including wound healing issues, nerve injury, and high recurrence rates [45]. These limitations have encouraged the development of less invasive strategies aimed at disrupting the collagen cords without open surgery [45]. Two of the most widely used alternatives are percutaneous needle aponeurotomy (PNA), which mechanically weakens the cord with a needle, and injections of collagenase clostridium histolyticum (CCH), an enzyme that breaks down collagen and softens the tissue [45]. Both methods are generally well tolerated, offer quicker recovery times, and allow many patients to regain finger extension with less downtime compared to surgery [45]. However, recurrence remains a challenge regardless of the technique, which raises the ongoing question of how to maintain long-term correction while minimizing complications and cost [45]. Understanding the biology behind cord formation, particularly the role of myofibroblasts and matrix dysregulation, may eventually allow for more targeted therapies that go beyond physical disruption and actually modify the fibrotic process itself.

Treating morphea presents ongoing challenges, largely because no single therapy works reliably across all subtypes or severities. Management often depends on how active or widespread the disease appears and focuses heavily on preventing long-term complications like joint contractures or deep tissue damage [46]. Unlike DD, where fibrosis is treated by directly targeting the cords, morphea requires systemic or immune-modulating approaches that aim to calm the underlying inflammatory response [46]. The difficulty in distinguishing between active disease and permanent skin damage adds another layer of complexity [46]. Tools like the Localized Scleroderma Cutaneous Assessment Tool (LoSCAT) have improved clinical monitoring by tracking features like skin thickening, redness, atrophy, and pigment changes, but consistent adoption remains limited [46]. Currently, the most widely used treatments are methotrexate and systemic corticosteroids, often given together [46]. High-dose steroid pulses are typically used to suppress inflammation early, followed by a maintenance phase with oral steroids and methotrexate [46]. In some cases, phototherapy, particularly UVA1, has been used to reduce collagen buildup and modulate cytokines that drive fibrosis [46]. This contrasts with Dupuytren's, where enzyme injections or mechanical disruption of cords target fibrosis locally [46]. In morphea, the diffuse nature of skin involvement and immune dysregulation makes treatment more complex and highlights the need for broader strategies that address both inflammation and matrix remodeling [46]. As research continues, the contrast in treatment approaches between these two fibrotic diseases serves as a reminder of how the same cellular players can create vastly different therapeutic challenges depending on tissue context.

4. Challenges And Limitations

4.1. Challenges in Diagnosing Dupuytren's Disease and Localized Scleroderma

There are nuanced differences in the molecular mechanisms that elicit the onset of Dupuytren's disease (DD) and localized scleroderma. Their respective clinical manifestations can be difficult to diagnose, which can inadvertently lead to implicit sample biases that are present in meta-analysis and case review studies. DD is a chronic disease of the palmar aponeuroses that progresses in stages, leading to the formation of nodules and extension deficit to the fingers [47]. However, due to its progressive, idiopathic nature, the visible staging of DD can prove difficult to diagnose until later stages. For instance, it is not until stage 2 that DD has an extension deficit between 45-90 degrees, allowing for clinical observation to guide a differential diagnosis of DD [47]. However, prior to this stage, there is only marginal functional loss and potential fibrosis [47]. Moreover, there are a multitude of different classification systems – including Meyerding, Tubiana, and Iselin – that are utilized in diagnosing the staging of DD, which can also blur the diagnosis of this disease with other diseases or conditions due to inherent

contradictions. For example, the Meyerding classification indicates that stage 1 DD showcases fibrosis without functional impairment, but the Tubiana classification explains that stage 1 acknowledges an extension deficit up to 45 degrees [47]. Therefore, clinical diagnoses, sample sizes, and statistics of DD may include potential errors due to diagnostic uncertainty.

Localized scleroderma also has an unknown etiology and is a rare, inflammatory skin condition that includes various variants that range from small, benign skin lesions to lesions that are aggressive and deformed [48]. Localized scleroderma is often visually diagnosed, and due to its vague and generalized skin symptoms as well as the absence of clear visual indicators, it is often common to misdiagnose with other mimickers [49]. For example, both DD at an early stage and localized scleroderma can include fibrosis of the hand, which can affect the population validity of research centered around localized scleroderma. Furthermore, localized scleroderma also takes on a multitude of modalities, such as plaque morphea, generalized morphea, bullous morphea, and linear scleroderma, offering nuance in effectively diagnosing this condition [50]. Beyond this, recent research has showcased that localized scleroderma is not exclusively cutaneous, and extends into the underlying tissue and organs, fostering an association with other connective tissue diseases [50]. As a result, clinical indicators between DD and localized scleroderma can often have visual parallels that can skew data and limit true samples of individuals diagnosed with these respective diseases.

4.2. Challenges in Experimentation

Several recent studies, literature reviews, and meta-analyses surrounding the prevalence and incidence of localized scleroderma predicate itself with outdated information. For example, Reiff et al. used information surrounding a study conducted by Peterson et al. about the epidemiology of localized scleroderma in one specific county [51]. The use of such studies is problematic due to their time relevance and the specific methodology used. Specifically, the analysis conducted by Peterson et al. involves screening 1,030 medical records and identifying 82 cases of localized scleroderma [34]. With such a limited sample size, it is difficult to generalize the calculated incidence and prevalence rate without incurring error and bias. Furthermore, the patient cases that were reviewed were only found in Olmsted County, which hinders its geographical validity as well. This is also seen in a study conducted by Toledano et al. in which only 52 patients were studied through a retrospective analysis [52]. Similarly, referencing a study that lacks population validity due to its low sample size likely does not acknowledge the true percentage of individuals and the distribution of symptoms that patients with localized scleroderma face.

This sheds light on a larger issue of the increasing difficulty to effectively diagnose localized scleroderma due to nuanced visual and clinical indicators. For example, as aforementioned, fibrosis is both a clinical indicator for both localized scleroderma and Dupuytren's disease (DD) at an early stage. Moreover, recent evidence reinforces that localized scleroderma is not simply cutaneous, but rather a disorder that can spread to underlying tissue and organs. The scope of differential diagnoses would extend to other underlying conditions, such as metabolic conditions like hypothyroidism or inflammatory and immune mediated conditions like eosinophilic fasciitis [49].

4.3. Challenges in Treatment

Both Dupuytren's disease (DD) and localized scleroderma are idiopathic in nature, indicating that there are a wide range of complex factors that impact the onset of both conditions. However, the management of both diseases is often unsatisfactory due to various challenges in establishing new treatments. Localized scleroderma has few randomized controlled studies revolving therapeutic agents [53]. Treatment is suggested to start early based upon the high morbidity that localized scleroderma has in limiting motion and bringing rise to deformities [50]. However, as aforementioned, the clinical indicators of early localized scleroderma are often vague and nuanced, which can cause issues in identifying markers to diagnose early. Although numerous clinical assessment methods have been published, such as induration, depigmentation, the modified Rodnan skin score, and the localized scleroderma skin severity index, these methods assess damage and activity based on limited clinical parameters [50]. Consequently, this not only renders it difficult for clinicians to effectively treat localized scleroderma due to the lack of validation on treatment response, but it also alters clinical response to localized scleroderma in practice.

For instance, dermatologists often treat localized scleroderma with topical agents and phototherapy, whereas pediatric rheumatologists

often use methotrexate or systemic corticosteroids [50]. However, no study has shown clinical and statistically significant efficacy in using high-potency topical corticosteroids for localized scleroderma [54]. Beyond this, experimental techniques, such as broadband ultraviolet light, have shown some promise in the treatment of localized scleroderma, but studies have shown that its exact benefits are unknown in its clinical management [55, 56]. As a result, it is clear that there is difficulty faced when diagnosing and treating localized scleroderma. The insufficient sample sizes underscores the need for additional research of this disease to improve on the matter.

Similarly, there are a multitude of challenges that are present in the treatment regimen of treating DD as DD remains influenced by a wide variety of factors, such as alcohol intake, smoking, and other established risk factors [57]. Most notably, there have been no reliable animal models that have been used to study the unique molecular mechanisms that onset DD, which have limited clinical and scientific efforts in examining different avenues that influence its onset. One such example is through *in vitro* studies, which use fibroblasts that have been isolated from Dupuytren cords or nodules against fascia that overlays the transverse carpal ligament or the carpal tunnel [58]. However, a key limitation involved in this approach is that the fascia overlying the carpal tunnel is rarely involved in Dupuytren contracture, which limits its efficacy in providing accurate knowledge surrounding the molecular bases behind the disease [59]. Scientific methodologies exploring DD are limited and inherently constrained due to the lack of effectively visualizing a potential therapeutic treatment of tissues involved in DD.

5. Future Directions

Standardizing fibroblast phenotyping is paramount in the advancement of the understanding and management of both Dupuytren's disease (DD) and localized scleroderma. Current literature indicates that fibroblasts play a critical role in the pathogenesis of these fibrotic conditions by their ability to regulate extracellular matrix production and modulate local inflammatory responses [60, 61]. Establishing a reliable and standardized framework for fibroblast phenotype classification can facilitate more focused research protocols, as well as encourage collaboration across specialties involved in the management of care associated with both DD and localized scleroderma [62]. Furthermore, the implications of a deeper understanding of fibroblast biology go beyond immediate clinical application, they may also direct future clinical trial direction, thereby resulting in the innovation of novel treatment modalities catered to particular patient phenotype profiles [60, 61, 63].

Cross-specialty collaboration remains essential for optimizing patient care in both DD and localized scleroderma. Specialists, namely rheumatologists, dermatologists, and hand surgeons (including both orthopedic surgeons and plastic surgeons) each offer complementary expertise that, when integrated, can enhance diagnostic precision and treatment outcomes. Rheumatologists, for instance, are well-positioned to evaluate both localized and systemic manifestations of scleroderma, utilizing tools like magnetic resonance imaging (MRI) and initiating immunomodulatory therapies like corticosteroids [64]. Dermatologists contribute diagnostic clarity through histopathological and serological evaluation, which often lead initial therapeutic measures with immunosuppressive agents tailored to cutaneous involvement [65]. These traditional "medical" management strategies form the foundation of acute and early-onset care. However, medical approaches alone may be insufficient in achieving longitudinal clinical improvement, especially in cases of advanced fibrosis or functional impairment [66]. As such, increasingly, patients are turning to surgical interventions, such as fasciotomy, needle aponeurotomy, open palmar fasciectomy, or collagenase injection, for symptomatic relief and restoration of hand function [64, 66, 67]. Such procedures, which bridge the gap between conservative and operative treatment modalities, are performed by hand surgeons, particularly those trained in orthopedics or plastic surgery [66, 67]. Emerging evidence also highlights the value of surgical decision-making that incorporates multidisciplinary input, particularly from dermatologists and rheumatologists, to align incision style and other surgical components with the broader clinical picture and disease trajectory [66].

Beyond clinical decision-making, cross-disciplinary collaboration also opens the door to collaborative research agendas, particularly in identifying and validating biomarkers that reflect fibroblast activity and fibrosis progression. These insights may illuminate novel therapeutic targets and inform the development of disease-modifying interventions that transcend the limitations of single-specialty perspectives [64,

68]. Ultimately, a sustained interdisciplinary approach not only enhances individualized care but also drives forward the collective understanding of fibrotic disease mechanisms, paving the way for innovation in both treatment and prevention strategies [66].

6. Conclusion

Dupuytren's disease (DD) is characterized by the uncontrolled growth of palmar fascia, marked by the increased deposition of type III collagen. Over time, activated myofibroblasts generate contractile forces that gradually pull the fingers into flexion. As the disease progresses, these changes culminate in the formation of dense fibrous cords. Localized scleroderma is an autoimmune connective tissue disorder characterized by an initial injury that induces inflammation and stimulates the production of autoantibodies. This inflammatory process drives the differentiation of fibroblasts into myofibroblasts, contributing to progressive deposition of type I collagen and resulting stiffness. Although DD and localized scleroderma differ significantly in clinical presentation, etiology, and prognosis, they exhibit strikingly similar underlying fibrotic features and fibroblast phenotypes. The first similarity is the excessive deposition of ECM and collagen, this is due to under expression of vital collagen breaking enzymes. The second is that myofibroblasts in both DD and localized scleroderma express α-smooth muscle actin, leading to their contractile properties. Lastly, there is widespread activation of the TGF-β pathway, while different downstream effectors are impacted they both lead to increased fibrosis and collagen deposition. Understanding these differences can allow us to explain why some fibrotic diseases remain localized while others are systematic.

Despite the similar fibrotic features and fibroblast phenotypes of DD and Localized scleroderma the treatments are extremely different. DD is traditionally treated with surgery to remove fibrotic tissue and free the tendons, or mechanically weakening the tendon with a needle while injecting collagenase clostridium histolyticum to weaken the collagen. In contrast Localized scleroderma is treated with immunosuppressants to treat systemic symptoms and UVA1 phototherapy for more localized treatment. This review highlighted the similarities and differences in fibroblast phenotypic plasticity between Dupuytren's contracture and localized scleroderma. While this research can answer some questions, future research is essential to understand how, despite these diseases being distinctively different, they operate utilizing the same mechanisms.

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