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Dupuytren's contracture

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Abstract

Dupuytren's contracture is a rare fibroproliferative disorder of the tissue beneath the palm of the hand that leads to finger contracture and may result in significant deformity and disability. There is no pharmacological treatment currently available for Dupuytren's contracture and surgery is advised when joint motion is impaired. However, surgical treatment poses some risks which could be overcome by early drug treatment. This review highlights the latest advances in understanding the pathophysiology of Dupuytren's contracture, as well as new treatment options currently under investigation.

Introduction

Dupuytren's contracture —named after Baron Guillaume Dupuytren, who provided the first anatomical study of this phenomenon in 1831— is a rare hand deformity caused by abnormal thickening of the fibrous tissue beneath the palm of the hand, which leads to contracture of the fingers, impeding the patient's ability to lay his/her palm flat. The initial pathognomonic sign is a firm, painless nodule that appears in the palmar fascia and is composed of fibroblasts and collagen. The nodule (stage 1) gradually forms a cord (stage 2) which contracts the metacarpophalangeal and proximal interphalangeal regions, finally resulting in digital contracture (stage 3) that can affect any digit, but which commonly involves the ring or little finger. The disease is usually unilateral, but bilateral affectation has also been observed. Dupuytren's contracture often presents with associated fibroproliferative manifestations in other body parts, such as knuckle pads (Garrod's nodes), plantar nodules (Ledderhose's disease) and penile fibromatosis, or Peyronie's disease (1).

Several factors have been typically associated with a greater risk of Dupuytren's contracture, including alcoholism, smoking, epilepsy and diabetes, but large epidemiological studies have generated some controversy as these associations lacked statistical significance (2, 3). Dupuytren's contracture affects more (and more severely) men and at a younger age than women. Although considered of sporadic onset, a higher prevalence of an autosomal dominant inherited form of Dupuytren's contracture has been observed, particularly in people from Northern European countries, associated with a single region on chromosome 16 (4). As will be discussed later, growth factor signaling pathways have been implicated in the pathogenesis of Dupuytren's contracture and several investigators have suggested that genetic variability in growth factor genes may be linked to an increased risk for developing this condition. However, the results of several studies have not shown a clear association. Thus, the presence of polymorphisms in transforming growth factor β-1 (*TGFB1*) and -2 (*TGFB2*) genes, which modulate fibroblast proliferation and differentiation and the expression of which is elevated in nodules of Dupuytren's contracture patients, have failed to show any association with an increased risk of Dupuytren's contracture (5, 6). A similar lack of correlation between polymorphisms in the TGF-β receptor (*TGFBR*) gene subtypes (II and III) and the risk of Dupuytren's contracture has been encountered (7). Only marginal significance was found for the *TGFBR1* risk allele in the recessive model, which requires further validation.

Pathophysiology

Role of contractile proteins

The pathognomonic sign of Dupuytren's contracture –the nodule– is the first clinical manifestation of fibroblast proliferation in the palmar fascia. Nodules, which can be multiple, are composed of fibroblasts and type III collagen. Once the nodule is well established, the contractile or involutional phase begins. Fibroblasts are replaced by myofibroblasts, which are contractile cells derived from fibroblast differentiation and are considered to be responsible for tissue contraction in Dupuytren's disease (8). The higher expression of contractile proteins such as α-smooth muscle actin (α-SMA) in myofibroblasts in

Dupuytren's tissue has been associated with increased cell contractility compared to non-Dupuytren's fibroblasts (9). Moreover, the expression of α-SMA is transient and correlates with the proliferative stage of the disease, being localized to nodule cells (10). Surprisingly, fibroblasts from cord tissue lack α-SMA, and therefore contractile ability, which poses the question of what causes the clinical phenotype of Dupuytren's contracture. Several hypotheses have been suggested, one of which is that the nodules generate the contractile forces required to pull the cord, which ultimately results in contracture of the phalangeal joints (10). *In vitro* treatment with platelet-derived growth factor (PDGF) has been shown to markedly reduce α-SMA content in Dupuytren's nodules (11).

Extracellular matrix dysregulation

Due to its fibroproliferative nature, researchers have investigated whether impaired extracellular matrix (ECM) degradation is involved in the pathogenesis of Dupuytren's contracture. In fact, the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), their endogenous inhibitors, is altered in the serum and palmar tissue from Dupuytren's patients (12). In particular, elevated levels of TIMP-1 were found to be significantly correlated with a lower MMP:TIMP ratio, which is common to other fibroproliferative conditions. In this study, serum MMP-1, MMP-2 and MMP-9 levels from Dupuytren's samples were not different from those of normal tissue. However, increased MMP-2 (gelatinase A) activation was described in palmar fascia tissue of Dupuytren's patients, with higher values in samples corresponding to early stages of disease progression, suggesting extensive ECM remodeling in this phase (13). However, the exact impact of this enzyme in disease pathogenesis remains to be established.

Another research group has reported upregulated expression of MMP-1, MMP-13 and MMP-14 in nodules from Dupuytren's patients, as well as elevated ADAMTS14 (a disintegrin and metalloproteinase with thrombospondin motif 14) and TIMP-1 expression compared to cord and normal control samples (14). These findings led to the hypothesis that fibrosis occurring in Dupuytren's contracture may arise from three factors: 1) elevation in ADAMTS14 (responsible for procollagen breakdown), which is consistent with increased collagen synthesis in the nodule; 2) increased TIMP-1, which would prevent collagenolysis via MMP-1 and MMP-13 inhibition; and 3) contraction due to MMP-14 (14). Additionally, extensive re-organization of ECM glycosaminoglycans such as dermatan sulfate has been also evidenced in palmar fascia tissue of patients with advanced disease (15), indicating that tissue remodeling in Dupuytren's contracture may be critical for disease pathogenesis.

Role of growth factors

As mentioned earlier, growth factors such as TGF-β have been implicated in the pathophysiology of Dupuytren's contracture. TGF-β, in addition to basic fibroblast growth factor (bFGF), regulates fibroblast and myofibroblast growth and differentiation, stimulates fibroblasts to synthesize and contract ECM, and also contributes to tissue fibrosis (16). The potential contribution of the two most common forms of TGF-β, TGF-β1 and TGF-β2, in Dupuytren's contracture has been studied. Stimulation of Dupuytren's tissue from nodules and cords with exogenous TGF-β1 increased the proportion of myofibroblast cells in both tissues, with a greater relative increase in cord samples, indicating that TGF-β1 was able to transform quiescent cord fibroblasts into myofibroblasts (17). This work also highlighted that, due to the high intracellular TGF-β1 content found in Dupuytren's nodules, local trauma occurring during surgery may cause TGF-β1 release to neighboring cord fibroblasts and prompt their transformation, hence increasing the risk of recurrence. However, another study revealed that exposure to high concentrations of TGF-β1 (15-30 ng/ml) was able to inhibit myofibroblast induction, thereby suggesting a feedback mechanism to limit contraction (18). Interestingly, an isolated report has shown that the antifibrotic molecule *N*-acetyl-L-cysteine may reduce markers of fibrogenesis in Dupuytren's fibroblasts via blockade of TGF-β1 signaling (19), which might have therapeutic implications.

As for TGF-β2, it has been suggested that it may upregulate collagen in Dupuytren's contracture tissue, thereby contributing to fibrosis progression (20). Also, increased TGF-β2 expression has been found in fibroblast-populated collagen lattices (FPCL), an investigational three-dimensional collagen structure mimicking the *in vivo* environment, from Dupuytren's patients, which was associated with a higher degree of fibroblast contraction compared to non-Dupuytren's controls. Interestingly, a response to tamoxifen treatment in Dupuytren's tissue was observed, with TGF-β2 downregulation and decreased fibroblast contraction (21). However, the role of TGF-β2 in Dupuytren's contracture has been challenged by others in a study where FPCL contraction was found to be independent of TGF-β2 (22).

Nerve growth factor (NGF) and epidermal growth factor (EGF) signaling may also be altered in Dupuytren's contracture according to different studies (23-25). However, results from these investigations are rather preliminary to confirm conclusively a link with disease pathogenesis.

Others

The cell adhesion molecule β-catenin, centrally involved in the canonical Wnt pathway which controls embryonic growth and development, has also been suggested to play a pathogenic role in Dupuytren's contracture (26). Studies have shown increased β-catenin and fibronectin levels in primary FPCL cultures derived from Dupuytren's contracture tissue, which are sensitive to changes in tension (27). However, elevated β-catenin did not correlate with changes in Wnt expression (28), sug-

gesting that alterations in Wnt signaling may not be the primary cause of β-catenin dysregulation in Dupuytren's contracture.

The *MAFB* gene, a member of the *MAF* proto-oncogene family involved in tissue development and cell differentiation, has also been found to be upregulated in palmar fascia cord tissue from Dupuytren's contracture patients and to be co-localized with α-SMA. *MAF* oncogenes were identified in an avian retrovirus that induced cellular transformation of fibroblasts *in vitro* and musculoaponeurotic fibrosarcoma *in vivo*, which resembles Dupuytren's disease histopathologically (29).

Studies on the gene expression profile of mature cords from Dupuytren's contracture patients have highlighted an increased expression of the receptor tyrosine kinase-like orphan receptor 2 (*ROR2*) gene (30). These authors suggested a potential role for *ROR2* in the differentiation state of Dupuytren's contracture cells, as *ROR2* is known to control chondrocyte and cartilage development. Moreover, mutations in *ROR2* have been associated with other hand deformity disorders, such as brachydactyly (31).

Treatment

The treatment of Dupuytren's contracture is usually delayed until hand function is impeded and surgery is usually required. It is generally recommended that patients undergo surgery as soon as digital contracture manifests (stage 3), because if contraction persists for a long time, irreversible ligament remodeling in that position may occur. Nevertheless, in recent years clinical research has centered on the pharmacological management of this disease.

Surgical treatment

Corrective surgery is recommended in Dupuytren's contracture to recover hand functionality. The most common surgical operations are fasciotomy and fasciectomy. Fasciotomy is a simpler procedure performed by dividing the cord but is associated with a higher recurrence rate, while fasciectomy consists of excising diseased palmar fascia. Fasciectomy can be either limited, when it involves only the removal of affected tissue, or total, if the all palmar fascia is extirpated. Surgery is commonly followed by hand physiotherapy to restore function and prevent rigidity (1).

Loos *et al*. have reported that amputation may be performed in advanced cases or when intraoperative ischemia occurs while performing corrective surgery. However, the introduction of a distraction device in 2003, called the Erlangen external extraction device, allowed elongation of the contracted soft tissue and distraction of the contracted joints prior to fasciectomy, hence preventing ischemic events (3). This study also reported low postsurgical complication rates and the preferred surgical technique was found to be limited fasciectomy (3).

As Dupuytren's contracture appears to be less prevalent in women, a retrospective case series review analyzed 109 consecutive female patients (119 hands) and compared them to 548 men (589 hands). Among different findings, researchers observed that women underwent surgery at an older age than men, although they presented with a similar clinical picture. Complication rates were comparable in both groups, although women reported less correction of the proximal interphalangeal joint (32).

Pharmacological treatment

1. Collagenase

Investigational therapies for Dupuytren's contracture mainly involve the use of clostridial collagenase, as collagen deposition has been implicated in disease pathogenesis. In an early *in vitro* study, cords obtained from Dupuytren's patients undergoing fasciectomy were injected with collagenase and the force required to rupture the cord was measured (33). A 300-unit dose of collagenase was the minimum effective dose associated with cord rupture, applying the average values of muscle tendon extensor force of normal fingers.

This was further tested in clinical studies with encouraging results. In an open phase II study, 29 Dupuytren's patients featuring 34 methacarpophalangeal (MCP), 9 proximal interphalangeal (PIP) and 1 thumb joint contractures received clostridial collagenase injections at a dose of 10,000 U. Collagenase treatment was found to be safe, with only minor local adverse events, and caused full extension recovery in 82% and 44% of MCP and PIP joints, respectively (34). The same research team conducted two other randomized, placebo-controlled clinical studies, one evaluating a fixed collagenase dose (10,000 U) *versus* placebo in 49 patients and the other consisting of a dose-response study where 80 patients received 2,500, 5,000 or 10,000 U of collagenase (35). The highest collagenase dose was corroborated as the minimum safe and effective dose to obtain a clinical response. In most patients, MCP and PIP joint contractures completely resolved, with joints recovering normal extension and improving finger motion with no affectation of flexion and grip strength. Adverse events were limited to local tissue reaction and were tolerated by patients. Repeated collagenase injection, which may be required in cases of multiple finger joint involvement, did not induce allergic reactions.

Auxilium Pharmaceuticals continues to develop clostridial collagenase for injection (AA-4500, Xiaflex®) for the treatment of patients with Dupuytren's contracture. In an initial randomized, double-blind phase III trial completed by 33 of 35 patients entered and followed by an open-label phase, 91% of patients treated with up to 3 injections of Xiaflex® achieved clinical success, with a reduction in joint contracture to within 0-5 degrees of normal; 86% of MCP and 100% of PIP joints were successfully treated. The open-label phase was conducted in 14 patients who were previously given placebo and 4 requiring additional collagenase injections, where 88% and 68% of MCP and PIP joints, respectively, resolved successfully. In addition, the recurrence rate was relatively

low, recurrence occurring in 5 joints (of 62 joints treated) between 12 and 24 months after treatment (36).

The promising therapeutic efficacy of Xiaflex® is being explored further by the company. A double-blind, placebo-controlled phase III clinical trial will be conducted in the United States –the CORD (Collagenase Option for Reducing Dupuytren's) study– in patients exhibiting MCP or PIP joint contractures in at least one finger other than the thumb of minimally 20 degrees, who will be randomized on a 2:1 basis to receive Xiaflex® or placebo (37, 38). The primary endpoint of the study is the reduction in joint contracture to within 0-5 degrees of normal after up to 3 injections of Xiaflex®. After trial completion, patients will be enrolled in a separate open-label extension study that will provide the opportunity for patients who failed initial treatment or who were given placebo to receive up to 5 injections of Xiaflex® (39).

A smaller phase III study following a similar protocol will also be conducted in Australia (the CORD II study) (40). Additional open phase III studies carried out by Auxilium are currently under way (37, 41). Xiaflex® is also being developed for Peyronie's disease and frozen shoulder syndrome (Auxilium Pharmaceuticals Web site).

2. Other treatment options

The antitumor agent 5-fluorouracil has also been proposed as a potential treatment for Dupuytren's disease. In fact, it is widely used during glaucoma surgery (trabeculectomy) to inhibit postoperative scarring (42). An *in vitro* study using fibroblast cultures prepared from primary Dupuytren's tissue treated with 5-fluorouracil demonstrated a selective and concentration-dependent down-regulation of collagen synthesis, with no effect on total protein synthesis. The endogenous secretion of TGF-β1 remained unaffected by 5-fluorouracil treatment (43). Despite these results, application of 5-fluorouracil in humans has rendered poor results. A small pilot study performed in 15 patients with Dupuytren's contracture in two digits revealed that intraoperative 5-fluorouracil treatment did not affect joint motion, finger extension or wound healing capacity compared to operated untreated digits (44).

Corticosteroid treatment with triamcinolone acetonide injections has also been used in Dupuytren's contracture with moderate success, as it did not appear to influence disease progression (45). The efficacy of triamcinolone acetonide is being further tested in a randomized open clinical study (46).

Conclusions

Although it is not a life-threatening condition, Dupuytren's contracture can progress to total loss of hand mobility and function, hence causing significant disability. Surgical procedures have been the mainstay of Dupuytren's management, as nonsurgical options tested have not shown significant benefits. With the current understanding of the pathogenic mechanisms underlying Dupuytren's contracture, pharmacological treatment with collagenase or other targeted therapies yet to come appears promising to avoid recurrence and complications associated with surgery.

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