Review

Advances in the understanding of the aetiology of Dupuytren’s disease

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Abstract

Dupuytren’s disease is a fibroproliferative disease of the palmar fascia which has been described for centuries, yet the aetiology and pathophysiology remain poorly understood. Surgery and collagenase injections comprise the main therapeutic options but disease recurrence is common. We explore the evidence underlying the current disease theories and outline other potential therapeutic options.

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Introduction

In 1831, a Parisien surgeon named Guillaume Dupuytren famously described a fibroproliferative condition of the palmar fascia which later became known as Dupuytren’s disease.1 This disease is characterised by a permanent, symptomatic thickening and shortening of the normal fibrous bands in the hand and fingers causing a flexion contracture. Most commonly, the ring and little finger metacarpophalangeal and proximal interphalangeal joints are affected. The epidemiology of the condition has been extensively described.2–3 Briefly, Dupuytren’s disease is most often seen in Caucasians of Northern European descent. It has been traced to a population of Germanic and Celtic tribes who migrated across Northern Europe centuries ago. The disease was then brought by emigrants to Australia and North America, the ‘New World’.4 In Iceland the disease prevalence is reportedly as high as 40% in males over the age of 70.5 Although some parts of Japan and Taiwan have an equal prevalence to Northern Europe, these patients present with a less disabling form of the disease whereby only nodules are present.6 In the UK, the overall incidence is around 4%, which rises to about 20% in those over 65 years.7 In 17% of cases in the UK, the disease is bilateral.8

The average age of Dupuytren’s disease onset is 60 years and the incidence increases thereafter. Men are more commonly afflicted, with a male:female ratio ranging between 3.5:1 and 9:1, although both sexes are affected equally after the age of 80 years.8 Bilateral disease is also more common in men, affecting 59% of men versus 43% of women.10 The term “Dupuytren’s diathesis” is used to describe patients with a particular susceptibility to the disease, who often present at
a younger age. They tend to have a strong family history and present with an aggressive form of the disease displaying bilateral manifestations including skin involvement and ectopic disease as well as a high recurrence rate postoperatively.

Although Dupuytren’s disease has been described for over 200 years, the molecular pathology is still poorly understood. Several environmental factors are thought to be associated with the disease including alcohol, smoking, diabetes, epilepsy, hypercholesterolaemia and injury but none of these have been shown convincingly to be causative. Moreover, the current treatment modalities tend to be invasive and purely symptomatic, associated with a high risk of recurrence. This review article will discuss the clinical presentation and the current understanding of the disease process as well as potential therapeutic interventions.

**Clinical presentation**

In early Dupuytren’s disease, the subcutaneous fat of the palm becomes fibrotic, resulting in thickening and adhesion of the skin to the underlying fascia. Pitting of the skin may occur as a result of contraction of the longitudinal palmar fascia fibres. These changes start in the palm and progress distally to the fingers as the palmar fascia is continuous with the digital fascia. Most often, the ring finger is involved first, followed by the small finger, then the thumb and other fingers. Either hand may be involved; one is usually more severely affected than the other. There is no relation to handedness.

Small, elevated firm tissue masses known as nodules arise from the superficial bands of the palmodigital fascia and are sometimes painful. As the disease progresses, these give way to the formation of cords which adhere to the skin. Most cords occur in the palm and over time they can resemble pseudo-tendons. The pretendinous cord is most frequently seen, which develops from the pretendinous band. The origins and anatomy of cords have been extensively described previously. Contraction of the palmar and digital cords occurs over months to years and can lead to fixed contractures of the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints respectively. Such deformity of the hand can severely restrict hand function, and diminish quality of life. Patients may complain of pain or reduced power with gripping. Ectopic disease may also develop, manifesting as Garrod’s nodes or knuckle pads. Often associated with bilateral disease, these are fibrosing dermal lesions located over the dorsal proximal interphalangeal joint. Patients who have Garrod’s nodes also have a higher rate of concurrent ectopic disease, for example, Lederhose disease (plantarfibromatosis) or Peyronie disease (penile fibromatosis).

It is worthwhile to note that since contractures are not always involved, the term “Dupuytren’s disease” rather than “Dupuytren’s contracture” is now used.

**Pathophysiology overview**

Dupuytren’s disease has been described as an exaggerated wound healing response, as the diseased tissue shows similar histological and biochemical alterations to those seen in the active stages of connective tissue wound repair. High numbers of myofibroblasts are observed, as well as increased extracellular matrix (ECM) deposition. Luck characterised three stages of the disease; proliferative, involutional and residual. During the proliferative phase, it is thought that the uncontrolled proliferation of myofibroblasts leads to the formation of nodules, resembling fibromas. This is now thought to occur under the influence of local mediators such as transforming growth factor (TGF-β1) and periostin. Originating in or superficial to the palmar fascia, the nodules expand towards the surface, replacing subcutaneous adipose tissue and attaching to the deep layers of the skin. Within these highly vascularised nodules, myofibroblasts show no apparent arrangement and do not align with lines of stress. It is important to note that these histological nodules do not necessarily correlate with the clinical ones noticed by the patient which can sometimes arise from the bunching up of the skin with contraction of the underlying fascia.

During the involutional phase the nodules become smaller, firmer and less defined. Myofibroblasts align along the major lines of stress that pass through the nodules, mostly in the longitudinal axis of the hand on the ulnar side. Myofibroblasts have morphological features of fibroblasts and smooth muscle cells and synthesize collagen, alpha-smooth muscle actin and fibronecin. There is an increased proportion of collagen type III, usually absent in adult palmar fascia, resulting in the formation of diseased cords. Actin microfilaments are organised into bundles parallel to the long axis of the myofibroblast. The bundles are continuous with extracellular fibrils of fibronecin along the myofibroblast surface which help form an attachment site called a fibronexus. In this way the contractile force of the intracellular actin is transmitted to the extracellular tissue. Abnormal collagen cross-linkage, together with the contractile forces generated by myofibroblasts, result in the early formation of contractures.

During the residual stage, nodules disappear leaving hypocellular and tendon-like thick fibrous cords. Cords may shorten and become more pronounced, causing further flexion contracture of MCP and PIPJs. In this later stage of Dupuytren’s disease, type III collagen decreases. Surgically resected DD cords are seen to contain both cell-dense and relatively acellular units (“nodule-cord unit”).

The cause of the myofibroblast proliferation in Dupuytren’s disease is still debated. The microvessels within Dupuytren’s tissue are considerably narrowed with many layers of basal laminae, similar to the microvessels seen in diabetic patients. It has been suggested that this provides hypoxic conditions activating the xanthine oxidase pathway. Xanthine oxidase acts as a catalyst for the oxidation of hypoxanthine to xanthine and uric acid. This conversion results in the production of free radicals which are thought to stimulate myofibroblast proliferation and cytokine release with the initiation of the disease process. The production of collagen leads to further hypoxia, thereby starting a vicious cycle. In support of this theory, the palmar fat lipid composition is compatible with mild hypoxia and high levels of free radicals are seen in Dupuytren’s tissue which induce fibroblast proliferation in vitro. Another study
has found that patients taking the drug Allopurinol, an inhibitor of xanthine oxidase had improvements in their contractures.
Conversely however, gout sufferers treated with allopurinol have not shown a lower prevalence of Dupuytren’s disease than the normal population.7

The theory of hypoxia does explain some of the epidemiological associations of the disease. For example, increasing age, Caucasian race, cigarette smoking and diabetes are all associated with microvessel narrowing and alcohol can mediate the conversion of xanthine dehydrogenase to xanthine oxidase.24 Acute penetrating injuries and smoking are also associated with free radical generation.28

Despite many attempts to identify their origin, the exact source of the myofibroblasts in Dupuytren’s disease also remains unknown.29 Many believe that resident fibroblasts in the palmar fascia are stimulated by cytokines and growth factors such as TGF-β1 and periostin to undergo differentiation into a nodule of myofibroblasts.8,17 Alternatively, as the structural components of the disease (cord, nodule, perinodular fat and skin) have been shown to contain distinct stem cell populations, it has also been hypothesized that Dupuytren’s disease may result from mesenchymal progenitor cell expansion.29,30 The implication of the palmar fat and skin in the pathogenesis of the disease could explain the fact that dermofasciectomy (excision of skin and subdermal fat) leads to reduced recurrence rates compared to fasciectomy alone.31

The mechanism by which the disease progresses from a nodule to a collagenous disease cord is also not understood. One hypothesis is that disease progression may be mediated by the proliferation and outward migration of disease cells from within the nodule to populate the adjacent palmar fascia, resulting in a disease cord containing contractile cells derived from the nodule. An alternative explanation is that nodular cells may secrete disease-associated factors into the surrounding ECM, altering its composition and triggering quiescent, phenotypically normal cells in the fascia to take on a proliferative, contractile phenotype.32 This could then explain how when the modified ECM is left behind after surgical resection of the DD cord, there is potential for the secreted factors to activate fibroblasts resident in the adjacent fascia to differentiate into myofibroblasts and promote disease recurrence.

Cytokines, growth factors and ECM components

A milieu of cytokines and growth factors has been implicated in the aetiology of Dupuytren’s disease. Several studies have documented TGF-β expression in Dupuytren’s palmar fascia using reverse transcriptase polymerase chain reaction (RT-PCR),33 in situ hybridisation34 and immunochemistry.35 TGF-β1 has been demonstrated to have a widespread intracellular localisation in myofibroblasts in all stages of Dupuytren’s disease as well as in normal fibroblasts in control palmar fascia. The TGF-β2 isoform is localised intracellularly in myofibroblasts during the proliferative and involitional disease stages but is absent in the residual stage, as well as being absent in control palmar fascia.35 Both isoforms are stimulators for myofibroblast proliferation, particularly TGF-β2. TGF-β was shown by immunohistochemistry to induce the expression of smooth muscle actin suggesting a role in fibroblast differentiation.36,37 In a released collagen lattice contraction assay, TGF-β1 was also shown to increase the force of contraction.38 Furthermore, results from other studies have suggested that TGF-β may promote chemotaxis and the synthesis of collagen and fibronectin.40 Tamoxifen has been demonstrated in vitro to decrease the function of fibroblasts from diseased fascia and downregulate TGF-β2 production, suggesting a potential method of manipulating Dupuytren’s contracture clinically.41

Platelet-derived growth factor (PDGF)-α and β are also found elevated in Dupuytren’s disease compared to healthy tissue.33 PDGF binds to cell membrane receptors on myofibroblasts and has been shown to be a potent inducer of cell proliferation with dose-dependent mitogenic effects.43 It is also thought to increase type III collagen synthesis,44 allow reorganisation of actin filaments and stimulate the production of arachidonic acid which can be converted to prostaglandin.45 PDGF does however significantly reduce the content of SMA in Dupuytren cells which may be a homeostatic mechanism to counter the upregulating effect of TGF-β.37

Other cytokines proven to stimulate fibroblast growth include interleukin-1 (IL-1), insulin-like growth factor (IGF) and fibroblast growth factor (FGF). Moreover, IL-1 can via its receptor, upregulate the production of TGF-β, FGF, epidermal derived growth factor (EDGF) and PDGF.46

It is hoped that knowledge of cytokines involved in the disease process may help identify new strategies for non-surgical treatment. For example, interferon (IFN)-γ, produced by helper T lymphocytes has been shown by some immunofluorescence studies to block the TGF-β stimulation of SMA and suppress the differentiation of myofibroblasts. This holds promise for early treatment but further work is needed to fully elucidate the signalling pathways.

In recent years, work has focused on the ECM component, periostin, which is abundant in Dupuytren’s disease cord tissue compared to control tissues.17 Periostin has been shown to regulate apoptosis, fibroblast proliferation and differentiation, α-SMA expression and stressed fibroblast populated collagen lattice contraction of cells.17 Myofibroblasts utilise the P13 kinase/Akt signalling pathway to avoid apoptosis in abnormal scarring and periostin signalling promotes avoidance of apoptosis through this pathway.37

The Wnt gene family encode glycoproteins and extracellular signalling molecules and aberrations have been linked to diseases such as cancer. High levels of β-catenin, an integral component of the Wnt signalling pathway, have been found both in vitro and in vivo.48 It has been suggested that β-catenin may be involved in the disease pathology as high levels are known to enhance normal fibroblast motility and invasiveness. Also supporting a role for Wnt signalling is the microRNA expression profiles of fibroblasts and palmar fascia in Dupuytren’s affected patients compared to controls. These miRNA’s regulate the β-catenin pathway. Other studies have suggested that Wnt genes are unlikely to be involved, yet another study proposed that overexpression of β-catenin may be regulated by upstream wnt pathways.49,50

Results from clinical cancer trials have also demonstrated that broad-spectrum matrix metalloproteinase (MMP)
Genetics

Genetic susceptibility is a well-recognised aetiological factor. This is supported by epidemiological observations, as the disease prevalence is so high in people of Northern European origin and is only rarely seen in African and Asian populations. Observations from twin and family studies, looking at trends of Dupuytren’s diathesis in particular, have also supported a genetic basis. In the UK population, the risk of the disease is found to be 2.9 fold higher in individuals with an affected sibling than in the general population.54

Transmission is thought to follow an autosomal dominant pattern with variable penetrance.55 Questions have arisen as to whether this is a complex oligogenic or simple monogenic mendelian disorder.

In a study of a five generation Swedish family, a 6 cM region on chromosome 16q (between markers D16S419 and D16S3032) was positively linked with the disease although a causative gene could not be identified.56 A different paper however showed that the expression of a gene IRX6, located within this region, is upregulated in diseased tissue.57

Using DNA microarray technology to compare gene expression patterns quantitatively, another group found that 30 unique genes were upregulated and six unique genes downregulated by fourfold or greater in diseased tissue compared with control palmar fascia.58 These included genes such as fibronectin, transforming growth factor (TGF-β2), tenascin, collagen III, IV and VI, which are known to be involved in the disease. TGF-β2 expression was increased by 10–20 fold in cord tissue as demonstrated by real time quantitative PCR. This study also showed upregulated gene expression of MafB (musculoaponeurotic fibrosarcoma oncogene homologue B). MafB is a basic domain leucin-zipper (BZIP)-type transcription factor of the Maf family of onco-genes, which in other models has shown involvement in fibroblastic transformation. Immunohistochemical analysis revealed MafB nuclear staining in myofibroblasts of cord tissue but not in paracord fascia or control tissue.59 The gene POSTN, which encodes periostin has also been shown to be upregulated in Dupuytren’s disease.59

Increased activation or expression of TGF-β1 can be induced by the transcription factor Zf9 or mitochondrial alterations resulting from partial mitochondrial depletion or treatment with an inhibitor.15 Through PCR, one group found that susceptibility to Dupuytren’s disease was associated with a single nucleotide polymorphism of the gene encoding Zf9.60

Other groups found that susceptibility to the disease was also associated with a heteroplasmic mutation within the mitochondrial 16s ribosomal RNA region. Bayat et al. found this mutation in 90% of patients with a maternally transmitted inheritance pattern and in none of the controls.61 Mitochondria play a role in cell metabolism and apoptosis and it is known that defective mitochondria generate abnormally high levels of reactive oxygen species. It is thought therefore that this mutation may be important in the pathogenesis of Dupuytren’s disease through oxidative stress.

Some papers have suggested that errors in growth and regulation of fibroblasts may occur, resulting from chromosomal abnormalities similar to cells undergoing neoplastic changes. Trisomies of chromosomes 7 and 8 have been reported as well as loss of the Y chromosome but as these findings were noted in culture, they should be interpreted with caution.

Finally, Human leukocyte alleles are also associated with Dupuytren’s disease; these are discussed below.

Immunology

Individuals with Dupuytren’s disease, have been shown to have autoantibodies against collagen types I–IV.64 It is thought therefore that autoantibodies could be contributing to the pathogenesis behind the disease. It was also noted that after surgical intervention, autoantibodies became undetectable, presumably as the antigens were removed.65 Furthermore, immune cell infiltrates have been seen in the Dupuytren’s nodules, which suggests an unregulated immune response occurring at this early stage of disease progression.

The MHC or HLA system is a tightly linked cluster of genes which regulate intercellular recognition and discrimination between self and non self with a role in humeral and cell-mediated immune responses. MHC molecules act as antigen-presenting complexes and the set of molecules an individual possesses determines which antigens T lymphocytes will respond to. Numerous genetic associations have been made between specific HLA alleles and certain diseases such as scleroderma, sarcoidosis and hypertrophic scarring. Evidence for a role of the HLA system in Dupuytren’s disease emerged from a study showing that autoantibodies to denatured collagen type II were more prevalent in HLA-DR4 positive Dupuytren’s patients than the population.64 Another group found a positive association between Dupuytren’s disease and HLA-DRB3 and this was associated with increased levels of autoantibodies against elastin and types I to IV collagen.65 Brown et al. also identified that the presence of the HLA-DRB1’S genotype conferred a 2.3 times relative risk for the development of the disease.66 Furthermore, Dupuytren’s patients have an increased fraction of activated CD3+ DR + cells compared to healthy controls and this increases with disease severity.57 The HLA system may be an ideal target for identification of potential biomarkers of disease.
Other associations with Dupuytren’s disease

Androgens

Androgen receptors are also expressed in the Dupuytren’s nodules. Cells from Dupuytren’s patients have a higher expression of androgen receptors and when stimulated with 5α-dihydrotestosterone show higher rates of proliferation than controls.68 This suggests that androgens may be important for myofibroblast proliferation in Dupuytren’s disease and would explain in part, the male predominance of the disease.

Alcohol

In the past, high levels of Dupuytren’s disease had been noted in alcoholics and in patients with liver cirrhosis. A prospective study was undertaken in the late 1980’s looking at 432 hospitalised patients.69 Using multivariate analysis to control for confounding variables, a similar prevalence of the disease was found in alcoholic patients with and without liver disease. This concluded that alcohol, rather than liver disease was associated. In patients with chronic cirrhotic liver disease, the presence of the disease suggested an alcoholic cause with a 90% positive predictive value.7

The mechanism behind the association of alcohol and Dupuytren’s disease is unclear. As mentioned earlier, alcohol can mediate the conversion of xanthine dehydrogenase to xanthine oxidase, which can oxidise hypoxanthine, producing free radicals. It has also been suggested that alcohol may damage fatty tissue to provoke a fibrotic response or alter prostaglandin production but none of these theories have been proven. Finally, two genes involved in alcohol metabolism were found to be downregulated in Dupuytren’s disease in one microarray analysis.70

Furthermore, despite the observed link between alcohol and Dupuytren’s disease, it must be remembered that most sufferers are not alcoholics. It could also be the case that heavy smoking is more common in alcoholic patients and it is this, rather than alcohol that explains the prevalence.

Epilepsy

Many studies investigated a link between epilepsy and Dupuytren’s disease and quoted varying incidences of the disease in this group of between 8% and 57%.71 The incidence seemed to increase with the severity of the disease.7 Moreover, people with epilepsy appeared to have a higher incidence of knuckle pads and plantar fibrosis. Epilepsy may therefore be associated with an increased susceptibility to fibrosing conditions through the disease itself or anticonvulsant medications. In fact, many papers have postulated a link between Dupuytren’s disease and anticonvulsant drugs, but the fact that non-white patients taking anticonvulsant medications do not show an increased risk, suggests otherwise. One recent case-controlled study found no association between Dupuytren’s disease and epilepsy or antiepileptic medications.72 As before, many studies have not been controlled for confounding variables and therefore must be interpreted with caution.

Diabetes

In 2004, Geohegan undertook a large case-controlled study which looked at a population in the West Midlands with Dupuytren’s disease compared to matched controls.72 Diabetes was noted to be a significant risk factor, particularly insulin-controlled diabetes and less so for diet controlled diabetes. This may be because of the increased severity of insulin-controlled diabetes or because it affects younger patients. Interestingly, Dupuytren’s disease in diabetic patients is associated with a lower incidence of contractures than in non-diabetics and many of the patients can be treated conservatively.73

The link is unclear as most diabetic patients do not suffer from Dupuytren’s contracture. Diabetes may act as a triggering factor. The high prevalence in diabetes may be due to the microangiopathy and increased collagen that is present. Of note, diabetics also have increased rates of flexor tenosynovitis and carpal tunnel syndrome, other inflammatory and proliferative processes of the hand.6

Smoking

Dupuytren’s disease has been reported to be three times higher in smokers which may be related to the microvascular changes providing hypoxic conditions, as discussed. One study showed that 68.2% of 132 Dupuytren’s patients were smokers compared to 37.2% of randomised hospital patients.74

Rheumatoid arthritis

Rheumatoid arthritis is the only condition that has been noted to be associated with a lower incidence of Dupuytren’s disease,75 although this may be due to the usage of anti-inflammatory drugs. Alternatively, it is thought that the rheumatoid hand deformities may mask the flexion deformities associated with Dupuytren’s disease.76

HIV infection

One study from the BMJ found that 36% of patients with HIV were affected by Dupuytren’s disease.77 All these patients had advanced infection and it was suggested that the presence of Dupuytren’s disease may be a marker of deranged free radical metabolism which may be an intermediary mechanism in the development of AIDS.

Trauma

Many patients with Dupuytren’s disease believe that their condition was caused by heavy labour or trauma. Dupuytren himself originally felt this to be the cause of the disease as many of the patients he studied were labourers. In an age where occupational injury-related litigation is increasing, it is important to delineate any associations. Melhorn and Ackerman reviewed 46 available studies and concluded that Dupuytren’s disease was associated with vibration but not with repetitive or forceful work in general.78 Another group noted that a history of vibration exposure or recurrent trauma...
resulted in a 5-fold increase in the incidence of Dupuyten’s disease, later supported by a meta-analysis in 2011. There have also been many reports of Dupuyten’s disease occurring after traumatic injury to the palm whereby the contracture develops at the site of injury. It is believed by some that trauma to the palmar fascia causes fibril ruptures in the collagen.

The association of the above factors in the etiology of Dupuyten’s disease is controversial. A large retrospective study conducted by Loos and colleagues on 2919 hands following surgery revealed that there was no statistically significant evidence that the occurrence of Dupuyten’s contracture could be correlated with the presence of diabetes, alcoholism or smoking. If associations do exist, no clear causal relationship has yet been proven.

Al-Qattan hypothesized that an individual who has a genetic predisposition to develop the disease experiences a second ‘hit’ or inciting event such as smoking, trauma, alcoholism or diabetes. This then results in microvascular ischaemia and the disease unfolds. Research continues into the pathology of this complex disease which appears multifactorial.

Research is also shifting towards identification of potential molecular targets for non-surgical treatments. One option is to remove the disease cords by enzymatic digestion of the cord, which Hueston in 1971 reported to be as successful as surgical fasciectomy. This involves the injection of a cocktail of proteolytic and anti-inflammatory enzyme (trypsin, hyaluronidase and lidocaine) to disrupt the collagenous environment. As the cords are composed of type I and III collagen, investigators have, more recently started to use a mixture of clostridium derived collagenases which target the NH2 and COOH terminals and internal peptide residues respectively in collagen fibres. As tendon and normal fascia are in close proximity and also contain collagen, the treatment needs to be localised. Studies have shown that collagenase injection into disease cords improves finger contractures and joint mobility in advanced disease. However, as this injection can target other collagenous structures of the hand, it is currently being evaluated for long-term safety. Furthermore, like surgery, the approach does not target the cause of the disease and recurrence is common.

Studies have shown that corticosteroid injections can function as antifibrotic agents to reduce cell proliferation and induce apoptosis. Although they can have been shown to soften nodules and reduce pain, steroids however, have well documented side effects.

As mentioned, IFN-γ also holds promise in providing a treatment option as it reduces cell proliferation, differentiation, SMA expression and collagen production. However, there have as yet been no good quality in vivo studies to investigate this potential treatment further.

Another potential treatment option involves the use of Imiquimod. This is an immune modulator that downregulates TGF-β and FGF-2, thought to be the two most important cytokines in producing fibrosis. Botulinum toxin has also been proposed as an intralesional treatment for the disease. It inhibits Rho GTPase, necessary for the activation of the IL-1 inflammation pathway. Studies investigating both these treatments are in the very early stages.

Conclusion

Currently the main risk factors involved in the pathogenesis of Dupuyten’s disease are family history, sex, age and ethnicity. It is unclear still whether the disease evolves due to hypoxia, altered immune responses, abnormal wound healing or a combination of factors. Currently surgical intervention is the mainstay of treatment although collagenase injections are showing promise. The importance of some disease associations such as epilepsy, remain controversial. It is hoped that a greater understanding of the disease mechanisms will remove some of this controversy and identify clear targets for future therapeutic intervention.

REFERENCES


