Scientific understanding and clinical management of Dupuytren disease

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Abstract | Dupuytren disease (DD) is a fibroproliferative disorder of unknown etiology that often results in shortening and thickening of the palmar fascia, leading to permanent and irreversible flexion contracture of the digits. This Review provides a detailed update of the scientific understanding of DD and its clinical management, with perspectives on emerging research and therapy. Established risk factors include genetic predisposition and ethnicity, as well as sex and age. Several environmental risk factors (some considered controversial) include smoking, alcohol intake, trauma, diabetes, epilepsy and use of anticonvulsant drugs, and exposure to vibration. DD has been variously attributed to the presence of oxygen free radicals, trauma to the palmar fascia, or aberrant immune responses with altered antigen presentation, or to interactions between these proposed mechanisms. The presence of immune cells and related phenomena in DD-affected tissue suggests that DD is possibly immune-related. Mechanically, digital contracture is caused by myofibroblasts in the DD palmar fascia; however, the exact origin of this cell type remains unknown. The mainstay of treatment is surgical release or excision of the affected palmodigital tissue, but symptoms often recur. Nonsurgical correction of DD contractures can be achieved by *Clostridium histolyticum* collagenase injection, although the long-term safety and recurrence rate of this procedure requires further assessment.

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Introduction

Dupuytren disease (DD) is a fibroproliferative disease that affects the palmar hand, causing progressive, permanent and symptomatic flexion contracture of the digits. The disease may cause deformity of the affected hand, limiting hand function and diminishing the patient's quality of life. DD is considered most common in whites of Northern European descent.[1] The average age at onset of disease is 60 years,[2] and the incidence increases with increasing age. DD occurs more often in men than in women, but the sex difference in prevalence diminishes with increasing age.[3] The prevalence of DD within different age groups and across geographical regions has been comprehensively reviewed elsewhere.[4]

As well as age and sex, a number of other factors, including ethnicity, family history and environmental factors, have been implicated in DD;[1,4–7] however, despite the condition first being described over 200 years ago (Box 1), our understanding of its pathogenesis is still unfolding. In addition, surgical treatment of DD is symptomatic and associated with a high rate of recurrence.[8] Better knowledge of the mechanisms involved could lead to more-effective and perhaps less-invasive therapies. This Review provides a detailed evaluation of the scientific understanding of DD—including genetic and immunological elements, molecular aberrations, environmental contributions and disease associations—and its clinical management, with perspectives on future and emerging research and therapy.

Competing interests
The authors declare no competing interests.

Disease description

The early stages of DD affect the bands of aponeurotic fascial fibers that run longitudinally in the palm. The so-called benign nodular and cord-like lesions of DD are often progressive and lead to shortening of the skin that retains and anchors ligaments, eventually progressing to permanent contracture of the affected digits (Figure 1).[9] Although some features of DD suggest a benign neoplastic (or quasineoplastic) process, DD is not considered a premalignant disorder.[1,10]

The histological and biochemical alterations in DD-affected tissue are similar to those in the active stages of connective tissue wound repair.[9,11] The tissue comprises high numbers of fibroblasts,[9] increased deposition of extracellular matrix (ECM) proteins (especially collagen)[12] and the presence of contractile myofibroblasts—a population of cells involved in the granulation stage of wound healing, which leads to wound contraction.[13]

On the basis of these morphological and cellular features, Luck[9] characterized three stages of DD presentation: proliferative, involutional and residual. The progression through these stages varies in different individuals and can be influenced by known risk factors. The proliferative stage is characterized by the presence of cellular fibroblastic nodules, within which the fibroblasts do not seem to present any apparent arrangements or align with lines of stress (Figure 2).[9] At this stage of the disease, cells, rather than collagen, make up a large portion of the tissue, and the nodules are likely to be vascular.[9] In the involutional stage, fibroblasts within the nodules align along the major lines of stress,

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Key points

- Genetic susceptibility, age, and ethnicity are the main risk factors for Dupuytren disease (DD); several environmental risk factors have also been implicated, although the evidence for some is controversial
- Epidemiological, familial, twin, and case–control studies support a genetic association for DD, and have identified susceptibility loci or genes, including those encoding transcription factor Zf9, mitochondrial 16s ribosomal RNA and HLA-DR alleles
- Several molecular aberrations have been observed in DD-affected tissue, relating to cytokines and growth factors, extracellular matrix proteins and associated molecules, and matrix metalloproteinases and associated proteins
- The pathophysiological mechanisms of DD are incompletely understood, but may be related to oxidative stress, altered wound repair and/or an aberrant immune response
- The mainstay of treatment for DD is surgery to relieve digital contractures, but this invasive intervention is associated with a high rate of disease recurrence
- Injection of *Clostridium histolyticum* collagenase effectively resolves DD contractures; however, the long-term recurrence rate and safety of this nonsurgical approach remain unclear

Box 1 | Dupuytren disease—a historical introduction

In 1777, the physician Henry Cline dissected flexion contractures in two subjects, noting that the contracted fingers immediately extended when the fascia were cut through. Cline's student Sir Astley Cooper further described the use of a procedure akin to needle fasciotomy for the treatment of this condition, and described the aponeurosis as the main cause of the observed palmar contraction. Cooper had several communications with and was visited by his contemporary Guillaume Dupuytren, a prominent Parisian surgeon who went on to describe the disease in a famous December 1831 lecture. In this lecture, later published in the journal *Lancet,* Dupuytren described the clinical features of digitopalmar contracture and its treatment in two of his patients. This publication in the medical literature ensured that the disease was named after him, and the eponym Dupuytren has been in clinical use ever since.

predominately in the longitudinal axes of the hand and commonly on the ulnar side.[9] As the contracture progresses, the nodules become smaller and increasingly ill-defined.[9] In the residual stage, the nodules disappear, leaving a hypocellular and tendon-like fibrous cord (Figure 2). Skin overlying the nodule can become fused with the underlying fascia and the cords may shorten, causing flexion contracture of the metacarpophalangeal joints (MCPJs) and proximal interphalangeal joints (PIPJs).[9] As a percentage of total collagen, type III collagen decreases in the latter stages of DD.[14]

Of note, the histological definitions of 'nodules' and 'cords' in Luck's classification differ from the clinical definitions, in which nodules are described as palpable, well-defined swellings, and cords are described as tight bands stretching across the palmar surface and/or joints causing flexion contractures. The Luck classification scheme has been adopted in DD research, but is not often used in clinical practice.

Genetics

Observations from twin studies and family studies suggest that DD has a strong genetic component.[15] DD aggregates in families, and individuals with a strong family history of DD may develop a more severe form of the disease and experience onset at a younger age.[7,16] Concordance has been demonstrated in monozygotic twins[15] and, furthermore, in a UK population the risk of DD was found to be 2.9-fold higher in individuals with an affected sibling than in the general population.[7] Studies characterizing DD prevalence and phenotype in different ethnic populations also suggest a geographic variation that is consistent with genetic predisposition.[15] The transmission of DD has been suggested to follow an autosomal dominant pattern with variable penetrance;[17] however, whether DD is a complex oligogenic or a simple monogenic Mendelian disorder is unclear.[17,18]

A 6cM region on chromosome 16q (between markers D16S419 and D16S3032) was positively linked with DD, although a causative gene for DD was not identified in this study.[19] A separate study, however, showed that the expression of a gene located within this region, *IRX6*, is upregulated in DD tissue.[20]

Case–control studies have explored the possible association between DD susceptibility and single nucleotide polymorphisms (SNPs) in the transforming growth factor (TGF)-β pathway, as the TGF-β pathway has been implicated in DD pathogenesis.[21–24] No association was found between DD and investigated SNPs in genes encoding TGF-β1,[18] TGF-β2,[25] and TGF-β receptors I–III,[26] although some regions of these genes that remain uninvestigated might still contain DD-causative polymorphisms or mutations.

Increased activation or expression of TGF-β1 can be induced by the transcription factor Zf9[27] or by mitochondrial alterations as a result of a partial mitochondrial depletion or treatment with a mitochondrial inhibitor.[28] Accordingly, DD susceptibility has been associated with a SNP within the gene encoding Zf9,[29] and with a heteroplasmic mutation located within the mitochondrial 16s ribosomal RNA region.[30] In addition, human leukocyte alleles (HLA) types have also been associated with DD, as discussed later in this Review.

Cytogenetic chromosomal aberrances have been described in cultures of DD-affected tissues. Multiple studies have reported trisomies of chromosomes 7 and 8,[31,32] abnormalities in these same chromosomes,[10] and loss of the Y chromosome.[32,33] However, because these chromosomal changes were observed in culture they should be interpreted with caution; for example, rather than causing DD, the observed changes might have resulted from the amplification of rare cells that are not related to DD but that have a selective advantage over normal cells in the *in vitro* environment.[10,33,34] Using array-based comparative genomic hybridization, Kaur *et al.*[34] did not identify any copy number variations (CNVs) or chromosomal imbalances in DNA from DD-affected tissue from 18 patients; the authors suggested that this inconsistency with findings from DD cultures could be due to DD-causative cells being present in low numbers

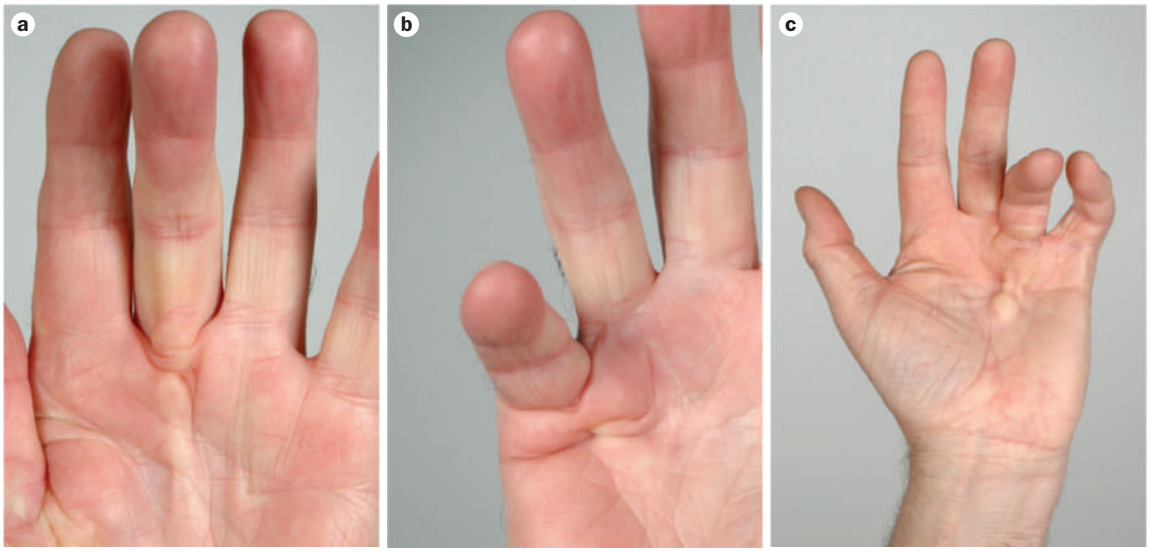

Figure 1 | Clinical presentation of Dupuytren disease. **a** | Early-stage DD affecting the palm and the base of the middle finger with a prominent cord and small nodules causing mild contracture of the MCPJ and minimal loss of extension, grip and strength. **b** | A more advanced stage of DD affecting the palm and the base of the fifth digit with an obvious pit (dimpling) at the base of the digit (but with a less prominent cord and nodule). Marked contracture of the MCPJ results in loss of extension of the fifth digit and reduced grip strength. **c** | Advanced-stage DD showing severe deformity. The disease affects the palm and the base of the fourth and fifth fingers with a prominent nodule and a tight cord causing marked contractures of the MCPJ and PIPJ of both digits, leading to a permanent fixed flexion deformity with loss of extension and reduced grip in the hand. Abbreviations: DD, Dupuytren disease; MCPJ, metacarpal phalangeal joint; PIPJ, proximal interphalangeal joint.

within the sampled tissues. A later study using a similar but higher-resolution technique identified several common regions of CNV in four DD patients, although a DD-associated CNV has yet to be determined.[35]

Immunology

Autoantibodies and antigen presentation

Autoantibodies against collagen types I–IV are reportedly present more frequently in the blood of patients with DD than from individuals without DD.[36–37] Neumüller *et al.*[36] suggested that autoantibodies may contribute to the pathogenesis of DD, and noted that autoantibodies in DD patients were no longer detectable several months after surgical intervention, possibly because removal of DD-affected tissues removed the antigen source.

The presence of autoantibodies can be associated with variation in genes involved in antigen presentation. Pereira *et al.*[37] reported that autoantibodies to denatured collagen type II were more prevalent in HLA-DR4-positive DD patients than the control population. On a different note, Neumüller *et al.*[36] found a positive association between DD and HLA-DRB3, as well as increased levels of autoantibodies against collagen and elastins in HLA-DRB3-positive individuals, which were higher in patients with DD compared with healthy controls. Three separate reports found no statistically significant associations between DD and HLA antigen distribution.[38–40] However, Spence and Walsh[41] noted a higher (although not statistically significant) incidence of HLA-DR4 in individuals with DD than those without. They also found that HLA-DR3-positive DD patients almost always carried *HLA-A1* and *HLA-B8* alleles, and argued that the HLA A1–B8–DR3 haplotype, which has also been associated with other autoimmune disorders, could be important in DD. Brown *et al.*[42] determined that the risk of DD was increased 2.3-fold in individuals with the *HLA-DRB1*15* genotype.

Immune cells

Various inflammatory and immune effector cells have been studied in DD, including macrophages,[43,44] lymphocytes,[45,46] dermal dendrocytes[44] and Langerhan cells,[47] with respect to both blood composition[46] and tissue infiltration.[43–45,47] Andrew *et al.*[43] noted that a large number of macrophages were present in the skin of a patient with DD. Another study[47] demonstrated an increased number of Langerhan cells in DD nodules and at the dermo-epidermal junction compared with healthy carpal tunnel tissue. Similarly, Sugden *et al.*[44] and Qureshi *et al.*[47] both identified factor XIIIa-positive cells in the skin, nodules, and blood vessels near nodules; however, the significance of these cells is unclear as they are also observed in normal tissues. MHC II-positive cells share similar morphology and distribution with factor XIIIa-positive cells in DD, suggesting that the observed factor XIIIa-positive cells might be activated cells of macrophage lineage.[44]

Complementary to the positive association of *HLA-DRB1*15* with DD reported by Brown *et al.*,[42] a few studies have described the distribution of HLA-DR-positive cells in patients with DD.[44–46] Increased expression of HLA-DR markers, which indicates expression of MHC class II molecules and an increased potential for antigen-presentation to T cells, has been associated with activated immune cells.[45] In a study of subcutaneous tissue from 14 patients with DD, HLA-DR antigen was present in 15–41% of non-adherent cells, compared

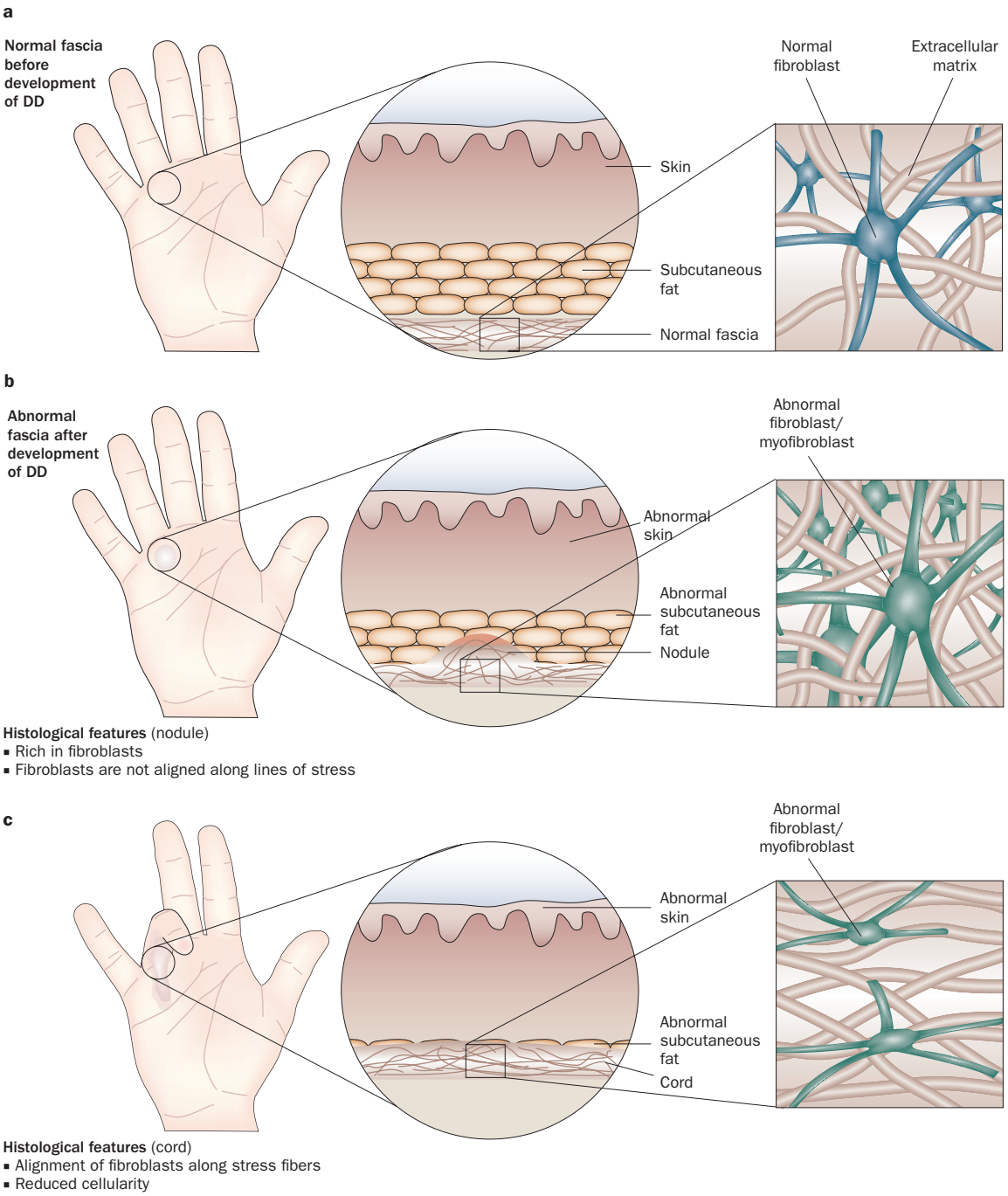

Figure 2 | Histological changes observed in Dupuytren disease. Compared with **a** | normal palmar fascia, **b** | the abnormal fascia in which DD nodules form is highly cellular with an increased amount of extracellular matrix. Fibroblasts within DD nodules do not align along stress lines in the early stages of the disease, but **c** | as the disease progresses and cords develop, cellularity is reduced and fibroblasts become aligned along the lines of stress. In addition, abnormal skin and subcutaneous fat have been proposed to be involved in the pathological process of the disease. Abbreviation: DD, Dupuytren disease.

with 1.2% non-adherent cells from the palmar fascia of individuals without DD undergoing carpal tunnel decompression.[45] In the blood of patients with DD, the fraction of activated ($CD3^+DR^+$) T cells and memory ($CD4^+CD45RO^+$ and $CD8^+CD45RO^+$) T cells is increased and the fraction of $CD5^+$ B cells is decreased in comparison with blood from healthy donors; these aberrances are more pronounced in patients with more-severe DD.[46]

Cytokines and growth factors

The expression of several cytokines, growth factors and their receptors are dysregulated in DD, including interleukin (IL)-1α,[48] IL-1β,[48] epidermal growth factor and its receptor,[49,50] basic fibroblast growth factor,[22,48,51] platelet-derived growth factor (PDGF)[52,53] and, as mentioned above, TGF-β (Figure 3; Table 1).[22,24] Immunocytochemical studies have associated PDGF

protein expression with myofibroblasts in the proliferative and involutional stages of DD,[52] and *PDGFB* expression has been detected in fibroblasts from biopsy-obtained samples of DD-affected tissues but not those of normal transverse palmar fascia.[53]

Levels of TGF-β transcripts in DD-affected tissues have been reported to be higher than those in fascia obtained from individuals undergoing carpal tunnel decompression.[48] Moreover, expression of the TGF-β2 isoform in DD cord tissues is higher than in unaffected control fascia.[24] The addition of exogenous TGF-β2 has been shown to increase the level of contracture in both DD and control fibroblasts cultured in a collagen lattice; however, neutralizing TGF-β2 did not seem to affect the elevated level of contracture observed in DD fibroblasts, suggesting that the contracture is not a result of higher levels of endogenous TGF-β2 in DD fibroblasts.[23] The TGF-β1 isoform intensely localizes within fibroblasts, myofibroblasts and capillary endothelial cells in all stages of DD, whereas intense intracellular localization of TGF-β2 occurs only within myofibroblasts in the proliferative and involutional stages.[21] In an *in vitro* primary cell culture model, type I collagen was implicated as a regulator of TGF-β1 signaling in DD pathogenesis.[54]

Other molecular aberrations

Aberrant expression or distribution of molecules involved in cell adhesion, ECM and interaction with ECM—including certain collagen types,[12,55–57] fibronectin isoforms,[11,22] α5β1 integrin,[58,59] periostin,[56,60–62] β-catenin,[63,64] glycosaminoglycans (GAGs),[65,66] proteoglycans,[61,67] and tenascin-C[56,61]—have been described in DD (Figure 3; Table 1). Elevated levels of β-catenin—an integral component of the Wnt signaling pathway—have been characterized in DD, both *in vitro* and *in vivo*.[63] Although mutations within exon 3 of the β-catenin gene have been associated with both deep and superficial fibromatoses, these mutations have not been observed in DD.[63,68] In addition, overexpression of β-catenin does not correlate with DD recurrence.[69] Varallo *et al.*[63] suggested that β-catenin may be involved in DD pathology since high levels of β-catenin enhance normal fibroblast motility and invasiveness; however, the results of a number of studies regarding the role of Wnt gene expression in β-catenin upregulation are conflicting.[69,70] Whilst one study[70] suggested that Wnt genes are unlikely to be involved in the β-catenin accumulation associated with DD, another study[69] suggested that overexpression of β-catenin might be regulated by upstream Wnt pathways. Increased expression of Wnt5a is found in DD during the involutional stage, which also shows an increased level of β-catenin.[69] The involvement of the β-catenin pathway has also been suggested by comparisons of microRNA profiles between samples from DD tissue and external controls.[64]

Elevated levels of total GAG content have been observed in DD tissues in recent studies,[65,66] although earlier studies had suggested the contrary.[67] Flint *et al.*[65] and Parry *et al.*[71] reported higher levels or percentages (of total GAG) of dermatan sulfate and chondroitin sulfate, as well as lower levels or percentages of hyaluronic acid,

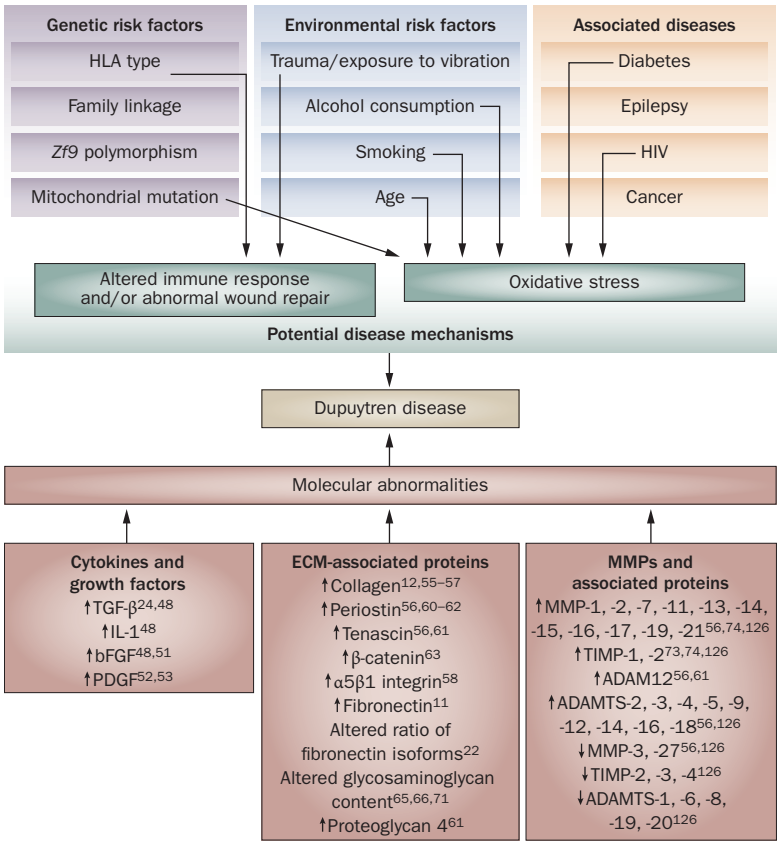

Figure 3 | Proposed mechanisms of and risk factors for Dupuytren disease. Risk factors associated with DD include genetic factors, environmental factors and disease association. The contribution of several of these risk factors to DD development has been ascribed to mechanisms involving altered immune responses, abnormal wound repair and oxygen tension. Aberrations in molecules involved in cytokine and growth factors, ECM-associated proteins, and MMPs and associated proteins are also thought to be involved in DD pathogenesis. Abbreviations: ADAM12, a disintegrin and metalloproteinase domain 12; ADAMTS, a disintegrin and metalloproteinase with a thrombospondin type 1 motif; bFGF, basic fibroblast growth factor; DD, Dupuytren disease; ECM, extracellular matrix; IL-1, interleukin-1; MMP, matrix metalloproteinase; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinase; Zf9, Kruppel-like factor 6.

in DD-affected tissues when compared with unaffected skin and fascia from the same individuals. With respect to small proteoglycans, DD-affected tissue has been associated with an accumulation of biglycan with small dermatan sulphate chains of high molecular mass, an increased amount of large chondroitin sulfate–dermatan sulfate proteoglycan, and changes in dermatan sulphate chain structures of decorin.[67]

The presence of different GAG molecules could affect collagen fibril density and diameter, and collagen fibrils in DD-affected tissues are of smaller diameter when compared with unaffected tissues.[71] An increased type III:type I collagen ratio has been noted in DD-affected fascia; type III collagen is virtually absent from normal palmar fascia but is abundant in DD tissues.[12] This difference in collagen-type ratio may be associated with upregulation of PDGF as well as TGF-β:[53] increased expression of type III collagen by mesangial cells is prevented by antibodies that neutralize PDGF or TGF-β and enhanced by the addition of PDGF or TGF-β.[72] Type I collagen could

Table 1 | Molecular aberrations reported in Dupuytren disease

Setting	Type of molecule			
	Cytokines and growth factors	Extracellular matrix and their associated proteins	MMPs and associated proteins	Other molecules
By location in tissue				
Nodule	Increased expression of IL-1α, IL-1β, bFGF and TGF-β[22,48]	Increased expression of type I collagen and other collagen types, α5β1 integrin, periostin, proteoglycan 4 and tenascin-C[55,56,58,61] Altered ratio of fibronectin isoforms[22]	Increased expression of TIMP-1, TIMP-2, MMPs, ADAM12 and ADAMTSs*[56,61,74,126] Decreased expression of TIMP-2, TIMP-3, TIMP-4, MMPs and ADAMTSs‡[56,126]	Increased expression of androgen receptors[81]
Cord	Increased expression of TGF-β2[24]	Increased expression of type I collagen, other collagen types and periostin[55,56] Involvement of β-catenin has been suggested[64]	Increased expression of TIMP-1, TIMP-2, MMPs, ADAM12 and ADAMTSs§[126] Decreased expression of MMP-3[126]	Increased expression of MafB[55]
Skin overlying nodule	NR	NR	NR	Higher glucose catabolic enzymes activities[100]
Fat	NR	NR	Increased expression of ADAM12[20]	Increased expression of ALDH1A1 and IRX6[20] Altered lipid composition[103]
By stage of disease				
Proliferative stage	TGF-β1 expressed in fibroblasts and myofibroblasts, and TGF-β2 expressed in myofibroblasts[21] PDGF expressed in myofibroblasts[52]	α5β1 integrin detected in the highly cellular areas and fibronectin expressed in the extracellular matrix[58,59]	NR	NR
Involution stage	TGF-β1 expressed in fibroblasts and myofibroblasts, and TGF-β2 expressed in myofibroblasts[21] PDGF expressed in myofibroblasts[52]	α5β1 integrin detected in the highly cellular areas and fibronectin expressed in the extracellular matrix; however, expression of the two molecules is absent in hypocellular areas[58,59]	NR	NR
Residual stage	TGF-β1 expressed in fibroblasts and myofibroblasts[21]	Decreased levels of fibronectin and α5β1 integrin[58,59]	NR	NR
Other				
Disease stage or location in tissue unspecified or other classification method used, or analysis performed in serum	Increased expression of PDGF in fascia[53] Decreased expression‖ of EGF in fascia[49] Higher ratio of surface:intracellular EGFR¶ in involutional stage compared with other stages[50] Increased levels of bFGF and its receptors[51]	Proteoglycan alterations# and increased expression of glycosaminoglycans[65–67] Type III collagen present in fascia that appears normal[12] Increased expression of β-catenin[63] Increased expression of periostin mRNA[60]	Increased expression of TIMP-1 and TIMP-2 in the proliferative areas of DD tissue[73] Levels of TIMP-1 in sera are higher in DD patients than in controls[73] Serum levels of TIMP-1 are higher in the proliferative stage than in the involutional or residual stages[73]	Increased expression of bone morphogenetic proteins in fibroblasts[79]

*Increased expression of MMP-1, MMP-2, MMP-7, MMP-11, MMP-13, MMP-14, MMP-15, MMP-16, MMP-17, MMP-19, MMP-21, ADAMTS-2, ADAMTS-3, ADAMTS-4, ADAMTS-5, ADAMTS-9, ADAMTS-12, ADAMTS-14, ADAMTS-16 and ADAMTS-18. ‡Decreased expression of MMP-3, MMP-27, ADAMTS-1, ADAMTS-6, ADAMTS-8, ADAMTS-19 and ADAMTS-20. §Increased expression of MMP-2, MMP-7, MMP-11, MMP-13, MMP-16, ADAMTS-3, ADAMTS-12 and ADAMTS-18. ‖Observed in first-degree and third-degree contracture, where first-degree contractures present with palmar tubercles and small cords but no contracture, and third-degree contractures affect the proximal interphalangeal joint. ¶Observed in second-degree contracture, defined as a bending contracture affecting the metacarpophalangeal joint. #Accumulation of biglycan with small dermatan sulphate chains of high molecular mass, increased amount of large chondroitin sulfate–dermatan sulfate proteoglycan, and changes in dermatan sulphate chain structures of decorin. Abbreviations: ADAM12, a disintegrin and metalloproteinase domain 12; ADAMTS, a disintegrin and metalloproteinase with a thrombospondin type 1 motif; bFGF, basic fibroblast growth factor; DD, Dupuytren disease; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; IL, interleukin; MMP, matrix metalloproteinase; mRNA, messenger RNA; NR, not reported; PDGF, platelet-derived growth factor; TGF, transforming growth factor; TIMP, tissue inhibitor of metalloproteinases.

be a regulator of β-catenin accumulation and a modifier of TGF-β1 signaling in DD cells, as suggested by Vi *et al.*[54] Elevated levels of periostin mRNA levels have also been reported in DD tissues in comparison with adjacent unaffected palmar fascia.[56,61–62] Moreover, incorporation of exogenous periostin into fibroblast-populated collagen lattice assays induces increased contracture and increased levels of α-smooth muscle actin (a marker for myofibroblasts) in DD fibroblasts compared with unaffected fascia fibroblasts.[62]

Various proteinases and their inhibitors that are involved in ECM degradation have been shown to be dysregulated in DD (Figure 3; Table 1). Patients with DD have higher serum levels of tissue inhibitors of metalloproteinase (TIMP)-1 in the serum than those without DD,[73] and those with proliferative-stage DD have higher levels of TIMP-1 than those with disease at the involutional or residual stage.[73] Increased amounts of TIMP-1 and TIMP-2 have been observed in proliferative areas of DD tissue, compared with little or no

expression in fascia obtained from individuals undergoing carpel tunnel decompression.[73,74] Increased expression of matrix metalloproteinase (MMP)-2 has been observed in DD tissues compared with control tissues and in DD tissues subjected to higher mechanical stress *in vitro*.[74–76] In addition to MMP levels being associated with DD recurrence,[77] treatment with ilomastat—an inhibitor of MMP—reduces contracture in a fibroblast-populated lattice assay, accompanied by reduced activity of MMP-1 and MMP-2 and increased activity of membrane type 1 MMP; the inhibition of contracture is most prominent in nodular fibroblasts.[78] Members of the ADAM (a disintegrin and metalloproteinase domain)[56,61] and ADAMTS (a disintegrin and metalloproteinase with thrombospontin motifs)[56,77] protein families have also been found to be dysregulated in DD and to be associated with post-surgical recurrence of DD.[56,61,77] Several other members of the MMP, ADAMTS and TIMP family have been reported to show aberrant expression in DD (Figure 3).[56,60] Other reported molecular aberrations in DD include bone morphogenetic proteins,[56,79] the transcription factor MafB,[55] tyrosine kinase-like orphan receptor 2,[80] myoglobin[80] and androgen receptors (Table 1),[81] but their roles in DD have not been explored in detail.

Environmental and other risk factors

Twins are not always concordant for DD, suggesting a possible role for environmental factors.[82] Several environmental factors have been proposed to contribute to DD development, including alcohol intake,[83–85] smoking,[83–85] manual labor or exposure to vibrations,[86] elevated blood glucose levels,[87,88] low body weight,[87] low BMI[87] and use of anticonvulsant drugs.[89] For instance, DD prevalence is linked with trauma or increased exposure to vibrations, and DD fibroblasts demonstrate less change in the peak cytosolic calcium response upon application of mechanical stress (laminar fluid flow) than normal fibroblasts.[90] Evidence for the association between DD prevalence and some of these environmental factors is, however, conflicting, as some studies have reported no statistically significant association between DD and alcohol intake,[91] exposure to vibration[92] or smoking.[91]

Nonetheless, DD has been associated with several other diseases, including epilepsy (and use of anticonvulsant medication),[89,92] diabetes mellitus,[84,88] HIV infection,[93] frozen shoulder[94] and cancer.[95,96] There is a 24% increase in overall risk of cancer in DD patients who have been surgically treated for DD that persists 10 years or longer after the operation in comparison with the risk in the general population.[95] A high incidence of DD has been reported in individuals with diabetes,[84] although the severity of diabetes did not correlate with DD incidence in a study by Noble *et al.*[88] Hart and Hooper[16] suggested that diabetes might only be a triggering factor for DD, based on the observation that DD in individuals with diabetes tends to be milder and rarely requires surgical intervention.[88] By contrast, more severe forms of DD with a high incidence of contractures have been observed in patients with epilepsy,[92] often bilaterally and symmetrically and associated with knuckle pads and plantar nodules in the foot.[89] From these observations, it has been suggested that an unknown mechanism may trigger a chronic fibrotic condition that develops into DD in some individuals upon exposure to anticonvulsant drugs.[16,89] Critchley *et al.*[89] proposed that the association between DD and anticonvulsant therapy is mediated through the stimulation of tissue growth factors at affected sites, rather than through the central release of growth hormone or alteration in liver metabolism. Regarding associations of DD with other diseases, Bower *et al.*[93] reported a higher prevalence of DD among patients with HIV compared with the general population, although this was not observed in a different cohort of patients with HIV investigated by French *et al.*[97] Notably, the incidence of DD is lower in patients with rheumatoid arthritis than in those without.[98] Hindocha *et al.*[4] have comprehensively reviewed the incidence of DD in relation to etiological factors.

Proposed disease etiology

DD nodules have been proposed to originate from or adjacent to the fascia, or aponeurosis.[9] As the disease progresses, the nodules expand towards the skin, displace subcutaneous fat and attach to the deeper layers of the skin.[9] The skin and subcutaneous fat overlying the fascia, however, might also be involved in DD pathogenesis and recurrence.[44,47,99] The activity of glucose catabolic enzymes is reportedly higher in the dermis overlying DD contractures than in normal palmar fascia.[100] In addition, a surgical treatment for DD that involves replacing the overlying skin, and that often removes adherent subcutaneous fat, is associated with a lower rate of recurrence than surgery without skin excision.[101] Subcutaneous fat might reduce trauma to the fascia by providing a cushioning, or shock-absorbing, effect.[102] Lower levels of subcutaneous fat tissue have been noted in individuals with DD in comparison with those without.[91] Low body weight and low BMI have also been associated with DD.[87] In addition, palmar fat in patients with DD is altered in composition in comparison to that from healthy controls, with DD fat being richer in free fatty acids, methyl esters of fatty acids and free cholesterols, containing less phospholipids and higher amounts of octanoate and other short-chain fatty acids.[103] Furthermore, three genes, *ADAM12*, *ALDH1A1* and *IRX6*, are differentially expressed in DD subcutaneous fat when compared with site-matched control samples from individuals undergoing carpal tunnel decompression.[20]

From histological examinations, Gabbiani and Majno[104] proposed that myofibroblasts are responsible for the digital contractures seen in DD. Tomasek *et al.*[105] noted that extracellular fibrils at the surface of DD myofibroblasts are in close association with intracellular bundles of actin microfilaments; these bundles extend from the myofibroblasts, connecting them with the surrounding matrix and other myofibroblasts.[105] The involvement of myofibroblasts in the remodelling of connective tissues has been previously reviewed.[13]

Lysophosphatidic acid (LPA) promotes DD fibroblast contraction in a dose-dependent manner,[106] and dependent on the regulation of myosin light chain phosphatase by Rho and Rho kinase.[107] Inhibitors of LPA-promoted

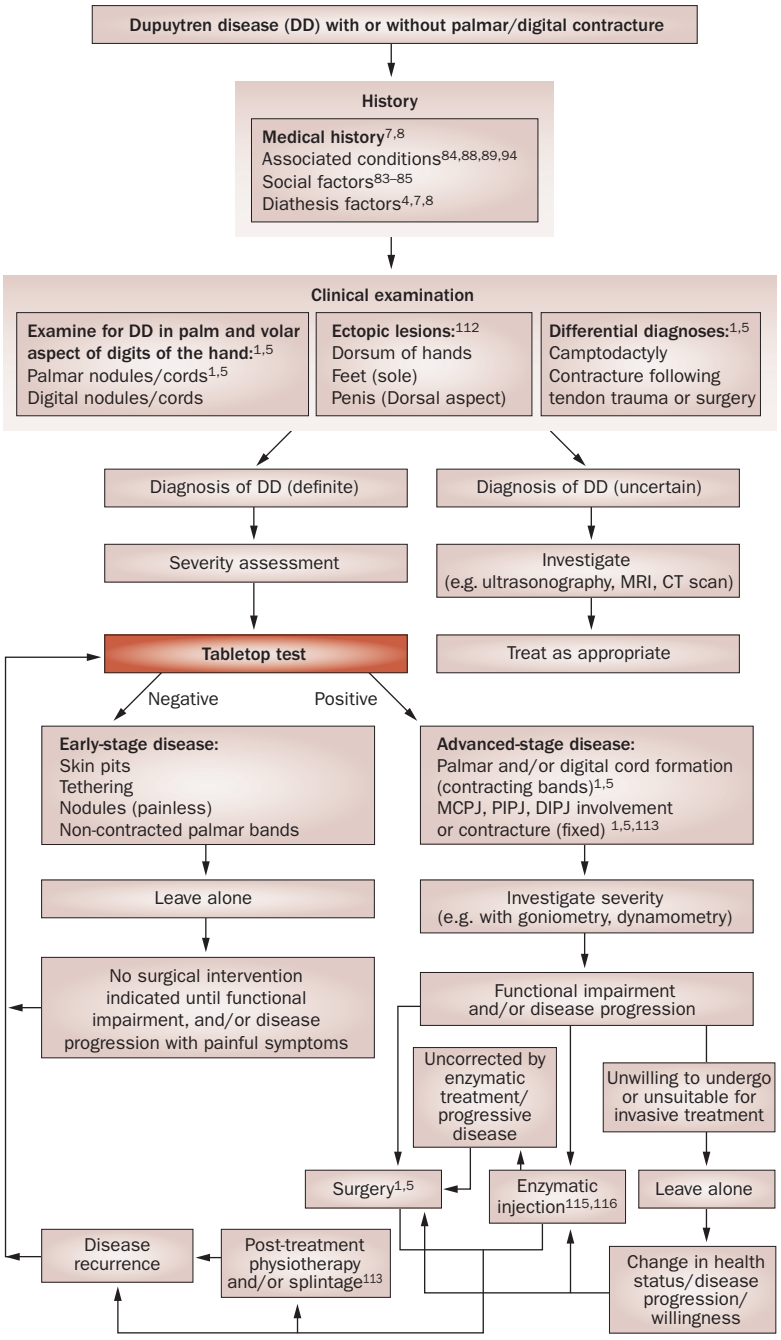

Figure 4 | Suggested algorithm for the assessment and treatment of Dupuytren disease. The management of DD involves a detailed clinical evaluation and assessment to determine the best course of treatment. Abbreviations: DD, Dupuytren disease; DIPJ, distal interphalangeal joint; MCPJ, metacarpal phalangeal joint; PIPJ, proximal interphalangeal joint.

contraction, including nifedipine, verapamil, prostaglandin E_1 (PGE_1) and PGE_2, have been proposed as potential drugs for DD.[106] Rayan *et al.*[106] suggested that increased LPA and decreased PGE may contribute to DD; however, higher levels of PGE_2 and $PGF_{2\alpha}$ have been reported in DD fascia.[108]

From the perspective of pathways involved in DD etiology, three major hypotheses have been proposed: altered immune response, abnormal wound healing, and the involvement of oxidative stress (Figure 3). A causative role for abnormal immune responses is supported by reports of aberrances in immunological elements in DD, including autoantibodies,[36,37] immune cells,[43–45,47] cytokines and growth factors,[22,24,48–50,52] and by the positive association between DD and *HLA-DRB1*15*.[42] The involvement of abnormal wound healing processes is supported by not only this altered immunity (the initial stage of wound healing involves an inflammatory response), but also aberrances in ECM proteins and their proteinases, the involvement of myofibroblasts—a key cell type involved in the final stages of wound healing—and the possibility that trauma and exposure to vibration increase the risk of DD.[13,86,90] In addition, biochemical changes and turnover in collagen have been described as similar to those that occur during wound repair.[12,57]

Mechanisms involving free radicals and oxidative stress have been proposed to explain the association between DD and each of diabetes, alcohol consumption and smoking.[109,110] Concentrations of hypoxanthine, which is involved in producing oxygen free radicals, has been found to be sixfold higher in DD tissues than in non-DD tissue.[109] The highest levels of hypoxanthine were detected in the 'nodular' area,[109] a highly proliferative area that some have proposed is the site of disease origin.[9] Murrell *et al.*[109] also demonstrated xanthine oxidase activity in DD-affected palmar fascia, although the level of this activity was not compared with that in samples from healthy individuals. Low concentrations of free radicals can induce skin fibroblasts to proliferate, and this proliferation is inhibited by free-radical scavengers in a dose-dependent manner.[110] The negative association between DD and rheumatoid arthritis might also support the involvement of oxygen free radicals,[98] as drugs involved in the treatment of rheumatoid arthritis may inhibit the effects of free radicals.[111]

Clinical management

Disease assessment

The management of DD involves a detailed clinical evaluation and assessment to determine the best course of treatment (Figure 4). The DD diathesis is used to assess prognosis and risk of recurrence. The diathesis includes ethnicity, family history of DD, age, sex and whether lesions are bilateral and/or occur at sites other than the hands.[8] Among other methods, disease severity is determined by the Hueston tabletop test, which determines whether the patient is able to place their palm flat on a tabletop, and the modified Tubiana staging system, which measures degree of contracture by goniometry and incorporates recurrence, number of affected digits, number of nodules, number of pits, presentation of other related disease and previous treatment.[112] Several features should be noted upon clinical examination: sites of nodules and bands or contracted cords, skin pitting, degree of skin involvement, measurement of the angle between the MCPJ and PIPJ, Garrod's nodes, surgical scars, sensation in the palm and digits, positive digital Allen's test, and presentation of secondary Boutonnière, swan neck or other digital deformities.[6]

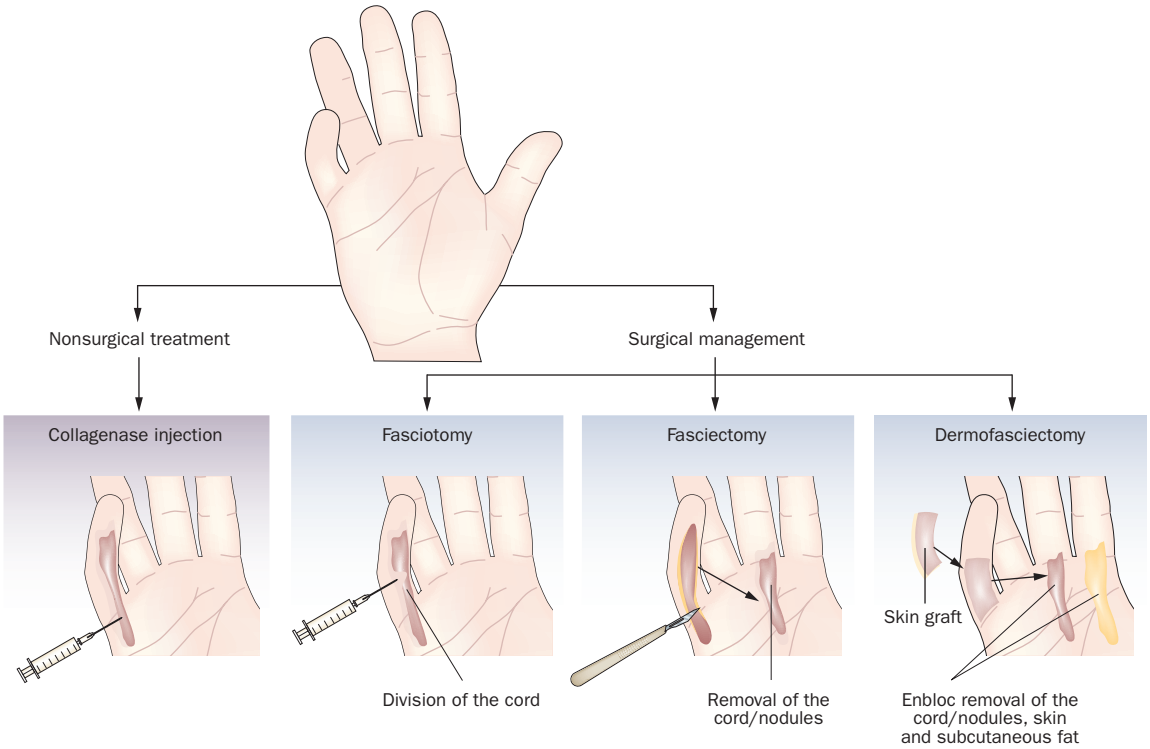

Figure 5 | Current and emerging treatments for Dupuytren disease. The three main surgical treatments for DD are fasciotomy (division, not removal, of the cord), limited fasciectomy (removal of DD-affected fascia), and dermofasciectomy (removal of DD-affected fascia and overlying skin and subcutaneous fat, followed by introduction of a skin graft). The use of enzymatic injection with the collagenase *Clostridium histolyticum* is emerging as a nonsurgical treatment for DD. Abbreviation: DD, Dupuytren disease.

Surgical treatment

Surgical intervention—with fasciotomy, fasciectomy or dermofasciectomy—is the current mainstay of treatment for DD (Figure 5).[4] No definitive threshold for surgical treatment exists, however, in terms of degrees of contracture of the digital joints. Most surgeons seem to set a surgical threshold of 40° flexion contracture in the MCPJs and 20° in the PIPJs.[113] In our experience, however, surgery should not be restricted to presentation with a certain degree of MCPJ or PIPJ contracture, but is indicated when the disease is functionally symptomatic or progressive, or both.[5]

Fasciotomy, performed percutaneously, surgically divides the cord to release the contracture without removing the cord, and is generally considered suitable for early-stage disease involving passively correctable flexion contracture in the MCPJs alone.[6] Fasciectomy removes the diseased palmar fascia, including the cord and nodule, via an open approach that can be limited, segmental or radical in extent for mild to moderate stages of primary disease.[6] Dermofasciectomy involves removal of the diseased palmar fascia (cord and nodule) and overlying affected skin; a full-thickness skin graft or skin substitute is usually employed to cover the defect in recurrent or severe disease.[5,7] In certain cases of longstanding advanced PIPJ contracture, external fixators can be used in addition to dermofasciectomy. Amputation can be a last resort for severe recurrent DD contractures despite previous surgical interventions. Variations of these surgical techniques exist, but a detailed discussion of the clinical management of DD, which has been comprehensively reviewed elsewhere,[114] is beyond the scope of this Review.

Nonsurgical treatment

The surgical treatment of DD is invasive, potentially involves a long recovery period and is associated with a high rate of recurrence, discussed in more detail below.[115] Several nonsurgical interventions have been evaluated in clinical trials, including *Clostridium histolyticum* collagenase injection (in phase II and III trials),[115,116] radiotherapy,[117,118] interferon-γ injection[119] and steroids.[120]

In a double-blind, placebo-controlled randomized phase III clinical trial, 308 patients with MCPJ or PIPJ contracture of 20° or more received up to three injections of *C. histolyticum* collagenase (0.58 g per injection) at 30-day intervals.[115] Compared with placebo, the treatment considerably reduced DD contractures and improved the range of motion in affected joints, with 92% of contractures of the MCPJ contractures being reduced to 30° degrees or less. *C. histolyticum* collagenase was approved by the FDA in February 2010 as an injectable treatment for DD.

Radiotherapy administered in the early stages of DD can prevent disease progression.[117,118] In a long-term follow-up of radiotherapy applied to early-stage DD (no extension deficit, or total flexion deformity of 1–5°), 70–87% of cases remained stable and showed no progression after 13 years.[118]

Post-treatment follow-up

Following treatment, two major issues demand consideration: rehabilitation and post-treatment complications. With respect to rehabilitation, most surgeons recommend post-surgery physiotherapy for all DD cases.[113] Many surgeons use dressing or splintage immediately after surgery, and most also recommend the use of night splintage;[113] however, the evidence for post-operative splinting is inconsistent. Rives *et al.*[121] found an improvement in the extent of PIPJ contracture in patients who undertook post-operative dynamic-extension splinting, whereas Ebskov *et al.*[122] concluded that this intervention did not influence the post-operative clinical outcome. A 2008 systematic review suggested that the level of evidence for the effects of post-operative splinting is low, and that a more extensive study is required to determine its clinical significance.[123] The main complication of DD treatment is the high rate of recurrence,[6] referring to the reappearance of DD in the region affected before treatment. Extension of the disease can occur in some cases, where new lesions are found in previously unaffected regions. Reported recurrence rates range widely, possibly as a result of differing interpretations of the term 'recurrence' and variation in the length of follow-up, as well as the use of diverse surgical methods. Detailed recurrence rates reported for each surgical method have been reviewed elsewhere; figures from some studies are listed as follows: 71% for fasciotomy, 50% for needle fasciotomy, 12.5% (at 2 years) to 71% (at 10 years) for partial fasciectomy, 5% (at 41 months) to 39.7% (at 47 months) for total fasciectomy, and 0% (at 80–100 months) to 8% (at 24–100 months) for dermofasciectomy.[124]

In an 8-year follow-up of collagenase injection in six patients treated for isolated MCPJ contracture and two treated for isolated PIPJ contracture, recurrence was observed in six of the eight cases. The recurrence in the MCPJ group was, however, generally less severe than the pre-injection contracture, and patient satisfaction with the procedure was high.[125] Studies with larger sample sizes are required to determine the recurrence rate and efficiency of collagenase treatment.

Other than recurrence, potential complications involved in the surgical treatment of DD include nerve damage, sympathetic dystrophy reflex, stiffness, infection, incomplete correction and loss of fingers.[113] Two cases of tendon rupture and one case of complex regional pain syndrome were reported following collagenase injection.[115]

Conclusions

DD is a common proliferative fibromatosis of unknown etiology. The main risk factors contributing to DD susceptibility include age, ethnicity, family history and sex. Major hypotheses suggested for the initiation of the disease include altered immune responses, local hypoxia and abnormal wound-healing responses. Although surgical intervention remains the mainstay of treatment, this approach is associated with complications and high recurrence rates. A number of non-invasive therapies have been effective and the use of *C. histolyticum* collagenase injection therapy by specialists hand surgeons seems promising but long-term follow-up data using a larger sample size are required to determine the safety and risk of recurrence with this approach. Further elucidation of the mechanisms involved in DD pathogenesis and a better understanding of the relationship of pathogenesis to etiology will continue to have an impact on the diagnosis, therapy and prognosis of the disease.

Review criteria

Articles included in this Review were retrieved by searching PubMed for relevant articles published in English up to September 2010, using the search terms "Dupuytren*", "major histocompatibility complex", "immune", "MHC", "human leukocyte antigen", "HLA", "autoantibodies", "collagen", "myofibroblast", "genetic susceptibility", "linkage", "inheritance", "oxidative stress", "oxygen tension", "free radicals", "hypoxia", "cigarette", "alcohol", "cytogenetic", "management", "cytokines", "MMP*", "matrix metalloproteinase", "female", "male", "ratio", "HIV", "Wnt", "rheumatoid arthritis", "population", "microarray" and "treatment", alone and in combination. Additional articles were identified from the references lists of the articles retrieved from PubMed.

1. Bayat, A. & McGrouther, D. A. Management of Dupuytren's disease—clear advice for an elusive condition. *Ann. R. Coll. Surg. Engl.* **88**, 3–8 (2006).
2. Stahl, S. & Calif, E. Dupuytren's palmar contracture in women. *Isr. Med. Assoc. J.* **10**, 445–447 (2008).
3. Anthony, S. G., Lozano-Calderon, S. A., Simmons, B. P. & Jupiter, J. B. Gender ratio of Dupuytren's disease in the modern U. S. population. *Hand (NY)* **3**, 87–90 (2008).
4. Hindocha, S., McGrouther, D. A. & Bayat, A. Epidemiological evaluation of Dupuytren's disease incidence and prevalence rates in relation to etiology. *Hand (NY)* **4**, 256–269 (2009).
5. Bayat, A., Cunliffe, E. J. & McGrouther, D. A. Assessment of clinical severity in Dupuytren's disease. *Br. J. Hosp. Med. (Lond.)* **68**, 604–609 (2007).
6. Bayat, A. & McGrouther, D. A. Dupuytren's disease. *Surgery* **24**, 373–375 (2006).
7. Hindocha, S., John, S., Stanley, J. K., Watson, S. J. & Bayat, A. The heritability of Dupuytren's disease: familial aggregation and its clinical significance. *J. Hand Surg. Am.* **31**, 204–210 (2006).
8. Hindocha, S., Stanley, J. K., Watson, S. & Bayat, A. Dupuytren's diathesis revisited: Evaluation of prognostic indicators for risk of disease recurrence. *J. Hand Surg. Am.* **31**, 1626–1634 (2006).
9. Luck, J. V. Dupuytren's contracture; a new concept of the pathogenesis correlated with surgical management. *J. Bone Joint Surg. Am.* **41-A**, 635–664 (1959).
10. Wurster-Hill, D. H., Brown, F., Park, J. P. & Gibson, S. H. Cytogenetic studies in Dupuytren contracture. *Am. J. Hum. Genet.* **43**, 285–292 (1988).
11. Howard, J. C. *et al.* Wound healing-associated proteins Hsp47 and fibronectin are elevated in Dupuytren's contracture. *J. Surg. Res.* **117**, 232–238 (2004).
12. Brickley-Parsons, D., Glimcher, M. J., Smith, R. J., Albin, R. & Adams, J. P. Biochemical changes in the collagen of the palmar fascia in patients with Dupuytren's disease. *J. Bone Joint Surg. Am.* **63**, 787–797 (1981).
13. Tomasek, J. J., Gabbiani, G., Hinz, B., Chaponnier, C. & Brown, R. A. Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat. Rev. Mol. Cell Biol.* **3**, 349–363 (2002).
14. Lam, W. L., Rawlins, J. M., Karoo, R. O., Naylor, I. & Sharpe, D. T. Re-visiting Luck's classification: a histological analysis of Dupuytren's disease. *J. Hand Surg. Eur. Vol.* **35**, 312–317 (2010).
15. Burge, P. Genetics of Dupuytren's disease. *Hand Clin.* **15**, 63–71 (1999).
16. Hart, M. G. & Hooper, G. Clinical associations of Dupuytren's disease. *Postgrad. Med. J.* **81**, 425–428 (2005).
17. Ling, R. S. The genetic factor in Dupuytren's disease. *J. Bone Joint Surg. Br.* **45**, 709–718 (1963).
18. Bayat, A. *et al.* Genetic susceptibility in Dupuytren's disease. TGF-β1 polymorphisms and Dupuytren's disease. *J. Bone Joint Surg. Br.* **84**, 211–215 (2002).

19. Hu, F. Z. *et al.* Mapping of an autosomal dominant gene for Dupuytren's contracture to chromosome 16q in a Swedish family. *Clin. Genet.* **68**, 424–429 (2005).
20. Shih, B., Brown, J. J., Armstrong, D. J., Lindau, T. & Bayat, A. Differential gene expression analysis of subcutaneous fat, fascia, and skin overlying a Dupuytren's disease nodule in comparison to control tissue. *Hand (NY)* **4**, 294–301 (2009).
21. Badalamente, M. A., Sampson, S. P., Hurst, L. C., Dowd, A. & Miyasaka, K. The role of transforming growth factor β in Dupuytren's disease. *J. Hand Surg. Am.* **21**, 210–215 (1996).
22. Berndt, A. *et al.* TGF β and bFGF synthesis and localization in Dupuytren's disease (nodular palmar fibromatosis) relative to cellular activity, myofibroblast phenotype and oncofetal variants of fibronectin. *Histochem. J.* **27**, 1014–1020 (1995).
23. Tse, R., Howard, J., Wu, Y. & Gan, B. S. Enhanced Dupuytren's disease fibroblast populated collagen lattice contraction is independent of endogenous active TGF-β2. *BMC Musculoskelet. Disord.* **5**, 41 (2004).
24. Zhang, A. Y. *et al.* Gene expression analysis of Dupuytren's disease: the role of TGF-β2. *J. Hand Surg. Eur. Vol.* **33**, 783–790 (2008).
25. Bayat, A. *et al.* Genetic susceptibility in Dupuytren's disease: lack of association of a novel transforming growth factor β2 polymorphism in Dupuytren's disease. *J. Hand Surg. Br.* **27**, 47–49 (2002).
26. Bayat, A., Stanley, J. K., Watson, J. S., Ferguson, M. W. & Ollier, W. E. Genetic susceptibility to Dupuytren's disease: transforming growth factor β receptor (TGFβR) gene polymorphisms and Dupuytren's disease. *Br. J. Plast. Surg.* **56**, 328–333 (2003).
27. Kojima, S. *et al.* Transcriptional activation of urokinase by the Kruppel-like factor Zf9/COPEB activates latent TGF-β1 in vascular endothelial cells. *Blood* **95**, 1309–1316 (2000).
28. Amuthan, G. *et al.* Mitochondria-to-nucleus stress signaling induces phenotypic changes, tumor progression and cell invasion. *EMBO J.* **20**, 1910–1920 (2001).
29. Bayat, A., Watson, J. S., Stanley, J. K., Ferguson, M. W. & Ollier, W. E. Genetic susceptibility to Dupuytren disease: association of Zf9 transcription factor gene. *Plast. Reconstr. Surg.* **111**, 2133–2139 (2003).
30. Bayat, A. *et al.* Identification of a novel mitochondrial mutation in Dupuytren's disease using multiplex DHPLC. *Plast. Reconstr. Surg.* **115**, 134–141 (2005).
31. Bonnici, A. V., Birjandi, F., Spencer, J. D., Fox, S. P. & Berry, A. C. Chromosomal abnormalities in Dupuytren's contracture and carpal tunnel syndrome. *J. Hand Surg. Br.* **17**, 349–355 (1992).
32. Dal Cin, P., De Smet, L., Sciot, R., Van Damme, B. & Van den Berghe, H. Trisomy 7 and trisomy 8 in dividing and non-dividing tumor cells in Dupuytren's disease. *Cancer Genet. Cytogenet.* **108**, 137–140 (1999).
33. Casalone, R. *et al.* Cytogenetic and interphase cytogenetic analyses reveal chromosome instability but no clonal trisomy 8 in Dupuytren contracture. *Cancer Genet. Cytogenet.* **99**, 73–76 (1997).
34. Kaur, S., Forsman, M., Ryhanen, J., Knuutila, S. & Larramendy, M. L. No gene copy number changes in Dupuytren's contracture by array comparative genomic hybridization. *Cancer Genet. Cytogenet.* **183**, 6–8 (2008).
35. Shih, B. B., Tassabehji, M., Watson, J. S., McGrouther, A. D. & Bayat, A. Genome-wide high-resolution screening in Dupuytren's disease reveals common regions of DNA copy number alterations. *J. Hand Surg. Am.* **35**, 1172–1183 (2010).
36. Neumüller, J., Menzel, J. & Millesi, H. Prevalence of HLA-DR3 and autoantibodies to connective tissue components in Dupuytren's contracture. *Clin. Immunol. Immunopathol.* **71**, 142–148 (1994).
37. Pereira, R. S., Black, C. M., Turner, S. M. & Spencer, J. D. Antibodies to collagen types I-VI in Dupuytren's contracture. *J. Hand Surg. Br.* **11**, 58–60 (1986).
38. Hunter, T., Shanahan, W. R. Jr, Robertson, G. A., Stranc, M. F. & Schroeder, M. L. The distribution of histocompatibility antigens in patients with Dupuytren's contracture. *Arthritis Rheum.* **24**, 1218–1219 (1981).
39. Tait, B. D. & Mackay, I. R. HLA phenotypes in Dupuytren's contracture. *Tissue Antigens* **19**, 240–241 (1982).
40. Williams, P. L., Dann, J., James, D. C. & Timlin, D. Histocompatibility antigens in subgroups of Dupuytren's contracture. *Br. J. Rheumatol.* **22**, 60–61 (1983).
41. Spencer, J. D. & Walsh, K. I. Histocompatibility antigen patterns in Dupuytren's contracture. *J. Hand Surg. Br.* **9**, 276–278 (1984).
42. Brown, J. J., Ollier, W., Thomson, W. & Bayat, A. Positive association of HLA-DRB1*15 with Dupuytren's disease in Caucasians. *Tissue Antigens* **72**, 166–170 (2008).
43. Andrew, J. G., Andrew, S. M., Ash, A. & Turner, B. An investigation into the role of inflammatory cells in Dupuytren's disease. *J. Hand Surg. Br.* **16**, 267–271 (1991).
44. Sugden, P., Andrew, J. G., Andrew, S. M. & Freemont, A. J. Dermal dendrocytes in Dupuytren's disease: a link between the skin and pathogenesis? *J. Hand Surg. Br.* **18**, 662–666 (1993).
45. Baird, K. S., Alwan, W. H., Crossan, J. F. & Wojciak, B. T-cell-mediated response in Dupuytren's disease. *Lancet* **341**, 1622–1623 (1993).
46. Gudmundsson, K. G., Arngrimsson, R., Arinbjarnarson, S., Olafsson, A. & Jonsson, T. T- and B-lymphocyte subsets in patients with Dupuytren's disease. Correlations with disease severity. *J. Hand Surg. Br.* **23**, 724–727 (1998).
47. Qureshi, F. I., Hornigold, R., Spencer, J. D. & Hall, S. M. Langerhans cells in Dupuytren's contracture. *J. Hand Surg. Br.* **26**, 362–367 (2001).
48. Baird, K. S., Crossan, J. F. & Ralston, S. H. Abnormal growth factor and cytokine expression in Dupuytren's contracture. *J. Clin. Pathol.* **46**, 425–428 (1993).
49. Augoff, K., Kula, J., Gosk, J. & Rutowski, R. Epidermal growth factor in Dupuytren's disease. *Plast. Reconstr. Surg.* **115**, 128–133 (2005).
50. Augoff, K., Tabola, R., Kula, J., Gosk, J. & Rutowski, R. Epidermal growth factor receptor (EGF-R) in Dupuytren's disease. *J. Hand Surg. Br.* **30**, 570–573 (2005).
51. Gonzalez, A. M. *et al.* Basic fibroblast growth factor in Dupuytren's contracture. *Am. J. Pathol.* **141**, 661–671 (1992).
52. Badalamente, M. A., Hurst, L. C., Grandia, S. K. & Sampson, S. P. Platelet-derived growth factor in Dupuytren's disease. *J. Hand Surg. Am.* **17**, 317–323 (1992).
53. Terek, R. M., Jiranek, W. A., Goldberg, M. J., Wolfe, H. J. & Alman, B. A. The expression of platelet-derived growth-factor gene in Dupuytren contracture. *J. Bone Joint Surg. Am.* **77**, 1–9 (1995).
54. Vi, L., Njarlangattil, A., Wu, Y., Gan, B. S. & O'Gorman, D. B. Type-1 collagen differentially alters β-catenin accumulation in primary Dupuytren's disease cord and adjacent palmar fascia cells. *BMC Musculoskelet. Disord.* **10**, 72 (2009).
55. Lee, L. C. *et al.* Expression of a novel gene, MafB, in Dupuytren's disease. *J. Hand Surg. Am.* **31**, 211–218 (2006).
56. Rehman, S. *et al.* Molecular phenotypic descriptors of Dupuytren's disease defined using informatics analysis of the transcriptome. *J. Hand Surg. Am.* **33**, 359–372 (2008).
57. Bazin, S. *et al.* Biochemistry and histology of the connective tissue of Dupuytren's disease lesions. *Eur. J. Clin. Invest.* **10**, 9–16 (1980).
58. Magro, G., Lanzafame, S. & Micali, G. Co-ordinate expression of α5β1 integrin and fibronectin in Dupuytren's disease. *Acta Histochem.* **97**, 229–233 (1995).
59. Magro, G., Fraggetta, F., Travali, S. & Lanzafame, S. Immunohistochemical expression and distribution of α2β1, α6β1, α5β1 integrins and their extracellular ligands, type IV collagen, laminin and fibronectin in palmar fibromatosis. *Gen. Diagn. Pathol.* **143**, 203–208 (1997).
60. Qian, A., Meals, R. A., Rajfer, J. & Gonzalez-Cadavid, N. F. Comparison of gene expression profiles between Peyronie's disease and Dupuytren's contracture. *Urology* **64**, 399–404 (2004).
61. Shih, B. *et al.* Identification of biomarkers in Dupuytren's disease by comparative analysis of fibroblasts versus tissue biopsies in disease-specific phenotypes. *J. Hand Surg. Am.* **34**, 124–136 (2009).
62. Vi, L. *et al.* Periostin differentially induces proliferation, contraction and apoptosis of primary Dupuytren's disease and adjacent palmar fascia cells. *Exp. Cell Res.* **315**, 3574–3586 (2009).
63. Varallo, V. M. *et al.* β-catenin expression in Dupuytren's disease: potential role for cell-matrix interactions in modulating β-catenin levels *in vivo* and *in vitro*. *Oncogene* **22**, 3680–3684 (2003).
64. Mosakhani, N. *et al.* Unique microRNA profile in Dupuytren's contracture supports deregulation of β-catenin pathway. *Mod. Pathol.* doi:10.1038/modpathol.2010.146.
65. Flint, M. H., Gillard, G. C. & Reilly, H. C. The glycosaminoglycans of Dupuytren's disease. *Connect. Tissue Res.* **9**, 173–179 (1982).
66. Tunn, S., Gurr, E., Delbruck, A., Buhr, T. & Flory, J. The distribution of unsulphated and sulphated glycosaminoglycans in palmar fascia from patients with Dupuytren's disease and healthy subjects. *J. Clin. Chem. Clin. Biochem.* **26**, 7–14 (1988).
67. Kozma, E. M., Olczyk, K., Wisowski, G., Glowacki, A. & Bobinski, R. Alterations in the extracellular matrix proteoglycan profile in Dupuytren's contracture affect the palmar fascia. *J. Biochem.* **137**, 463–476 (2005).
68. Montgomery, E., Lee, J. H., Abraham, S. C. & Wu, T. T. Superficial fibromatoses are genetically distinct from deep fibromatoses. *Mod. Pathol.* **14**, 695–701 (2001).
69. Degreef, I., De Smet, L., Sciot, R., Cassiman, J. J. & Tejpar, S. β-catenin overexpression in Dupuytren's disease is unrelated to disease recurrence. *Clin. Orthop. Relat. Res.* **467**, 838–845 (2009).
70. O'Gorman, D. B., Wu, Y., Seney, S., Zhu, R. D. & Gan, B. S. Wnt expression is not correlated with β-catenin dysregulation in Dupuytren's disease. *J. Negat. Results Biomed.* **5**, 13 (2006).
71. Parry, D. A., Flint, M. H., Gillard, G. C. & Craig, A. S. A role for glycosaminoglycans in the development of collagen fibrils. *FEBS Lett.* **149**, 1–7 (1982).

72. Throckmorton, D. C., Brogden, A. P., Min, B., Rasmussen, H. & Kashgarian, M. PDGF and TGF-β mediate collagen production by mesangial cells exposed to advanced glycosylation end products. *Kidney Int.* **48**, 111–117 (1995).
73. Ulrich, D., Hrynyschyn, K. & Pallua, N. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in sera and tissue of patients with Dupuytren's disease. *Plast. Reconstr. Surg.* **112**, 1279–1286 (2003).
74. Ulrich, D., Ulrich, F., Piatkowski, A. & Pallua, N. Expression of matrix metalloproteinases and their inhibitors in cords and nodules of patients with Dupuytren's disease. *Arch. Orthop. Trauma Surg.* **129**, 1453–1459 (2009).
75. Tarlton, J. F. *et al.* Mechanical stress *in vitro* induces increased expression of MMPs 2 and 9 in excised Dupuytren's disease tissue. *J. Hand Surg. Br.* **23**, 297–302 (1998).
76. Augoff, K., Ratajczak, K., Gosk, J., Tabola, R. & Rutowski, R. Gelatinase A activity in Dupuytren's disease. *J. Hand Surg. Am.* **31**, 1635–1639 (2006).
77. Johnston, P., Larson, D., Clark, I. M. & Chojnowski, A. J. Metalloproteinase gene expression correlates with clinical outcome in Dupuytren's disease. *J. Hand Surg. Am.* **33**, 1160–1167 (2008).
78. Townley, W. A., Cambrey, A. D., Khaw, P. T. & Grobbelaar, A. O. Matrix metalloproteinase inhibition reduces contraction by Dupuytren fibroblasts. *J. Hand Surg. Am.* **33**, 1608–1616 (2008).
79. Shin, S. S., Liu, C., Chang, E. Y., Carlson, C. S. & Di Cesare, P. E. Expression of bone morphogenetic proteins by Dupuytren's fibroblasts. *J. Hand Surg. Am.* **29**, 809–814 (2004).
80. Forsman, M. *et al.* The expression of myoglobin and ROR2 protein in Dupuytren's disease. *J. Surg. Res.* **15**, 271–275 (2008).
81. Pagnotta, A., Specchia, N. & Greco, F. Androgen receptors in Dupuytren's contracture. *J. Orthop. Res.* **20**, 163–168 (2002).
82. Lyall, H. A. Dupuytren's disease in identical twins. *J. Hand Surg. Br.* **18**, 368–370 (1993).
83. Godtfredsen, N. S., Lucht, H., Prescott, E., Sorensen, T. I. & Gronbaek, M. A prospective study linked both alcohol and tobacco to Dupuytren's disease. *J. Clin. Epidemiol.* **57**, 858–863 (2004).
84. Burke, F. D., Proud, G., Lawson, I. J., McGeoch, K. L. & Miles, J. N. An assessment of the effects of exposure to vibration, smoking, alcohol and diabetes on the prevalence of Dupuytren's disease in 97,537 miners. *J. Hand Surg. Eur. Vol.* **32**, 400–406 (2007).
85. Burge, P., Hoy, G., Regan, P. & Milne, R. Smoking, alcohol and the risk of Dupuytren's contracture. *J. Bone Joint Surg. Br.* **79**, 206–210 (1997).
86. Liss, G. M. & Stock, S. R. Can Dupuytren's contracture be work-related?: review of the evidence. *Am. J. Ind. Med.* **29**, 521–532 (1996).
87. Gudmundsson, K. G., Arngrimsson, R., Sigfusson, N., Bjornsson, A. & Jonsson, T. Epidemiology of Dupuytren's disease: clinical, serological, and social assessment. The Reykjavik Study. *J. Clin. Epidemiol.* **53**, 291–296 (2000).
88. Noble, J., Heathcote, J. G. & Cohen, H. Diabetes mellitus in the aetiology of Dupuytren's disease. *J. Bone Joint Surg. Br.* **66**, 322–325 (1984).
89. Critchley, E. M., Vakil, S. D., Hayward, H. W. & Owen, V. M. Dupuytren's disease in epilepsy: result of prolonged administration of anticonvulsants. *J. Neurol. Neurosurg. Psychiatry* **39**, 498–503 (1976).
90. Gupta, R. *et al.* The effect of shear stress on fibroblasts derived from Dupuytren's tissue and normal palmar fascia. *J. Hand Surg. Am.* **23**, 945–950 (1998).
91. Bergenudd, H., Lindgarde, F. & Nilsson, B. E. Prevalence of Dupuytren's contracture and its correlation with degenerative changes of the hands and feet and with criteria of general health. *J. Hand Surg. Br.* **18**, 254–257 (1993).
92. Arafa, M., Noble, J., Royle, S. G., Trail, I. A. & Allen, J. Dupuytren's and epilepsy revisited. *J. Hand Surg. Br.* **17**, 221–224 (1992).
93. Bower, M., Nelson, M. & Gazzard, B. G. Dupuytren's contractures in patients infected with HIV. *BMJ* **300**, 164–165 (1990).
94. Smith, S. P., Devaraj, V. S. & Bunker, T. D. The association between frozen shoulder and Dupuytren's disease. *J. Shoulder Elbow Surg.* **10**, 149–151 (2001).
95. Wilbrand, S., Ekbom, A. & Gerdin, B. Cancer incidence in patients treated surgically for Dupuytren's contracture. *J. Hand Surg. Br.* **25**, 283–287 (2000).
96. Wilbrand, S., Ekbom, A. & Gerdin, B. Dupuytren's contracture and sarcoma. *J. Hand Surg. Br.* **27**, 50–52 (2002).
97. French, P. D., Kitchen, V. S. & Harris, J. R. Prevalence of Dupuytren's contracture in patients infected with HIV. *BMJ* **301**, 967 (1990).
98. Arafa, M., Steingold, R. F. & Noble, J. The incidence of Dupuytren's disease in patients with rheumatoid arthritis. *J. Hand Surg. Br.* **9**, 165–166 (1984).
99. Hueston, J. The role of the skin in Dupuytren's disease. *Ann. R. Coll. Surg. Engl.* **67**, 372–375 (1985).
100. Hoopes, J. E., Jabaley, M. E., Su, C. T., Wilgis, S. & Im, M. J. Enzymes of glucose metabolism in palmar fascia and Dupuytren's contracture. *J. Hand Surg. Am.* **2**, 62–65 (1977).
101. Tonkin, M. A., Burke, F. D. & Varian, J. P. Dupuytren's contracture: a comparative study of fasciectomy and dermofasciectomy in one hundred patients. *J. Hand Surg. Br.* **9**, 156–162 (1984).
102. Flint, M. H. in *The Genesis of the Palmar Lesion.* (eds McFarlane, R. M., McGrouther, D. A. & Flint, M. H.) 140–145 (Churchill Livingstone, New York, 1990).
103. Rabinowitz, J. L., Ostermann, L. Jr, Bora, F. W. & Staeffen, J. Lipid composition and *de novo* lipid biosynthesis of human palmar fat in Dupuytren's disease. *Lipids* **18**, 371–374 (1983).
104. Gabbiani, G. & Majno, G. Dupuytren's contracture: fibroblast contraction? An ultrastructural study. *Am. J. Pathol.* **66**, 131–146 (1972).
105. Tomasek, J. J., Schultz, R. J. & Haaksma, C. J. Extracellular matrix-cytoskeletal connections at the surface of the specialized contractile fibroblast (myofibroblast) in Dupuytren disease. *J. Bone Joint Surg. Am.* **69**, 1400–1407 (1987).
106. Rayan, G. M., Parizi, M. & Tomasek, J. J. Pharmacologic regulation of Dupuytren's fibroblast contraction *in vitro*. *J. Hand Surg. Am.* **21**, 1065–1070 (1996).
107. Parizi, M., Howard, E. W. & Tomasek, J. J. Regulation of LPA-promoted myofibroblast contraction: role of Rho, myosin light chain kinase, and myosin light chain phosphatase. *Exp. Cell Res.* **254**, 210–220 (2000).
108. Badalamente, M. A., Hurst, L. C. & Sampson, S. P. Prostaglandins influence myofibroblast contractility in Dupuytren's disease. *J. Hand Surg. Am.* **13**, 867–871 (1988).
109. Murrell, G. A., Francis, M. J. & Bromley, L. Free radicals and Dupuytren's contracture. *Br. Med. J. (Clin. Res. Ed.)* **295**, 1373–1375 (1987).
110. Murrell, G. A., Francis, M. J. & Bromley, L. Modulation of fibroblast proliferation by oxygen free radicals. *Biochem. J.* **265**, 659–665 (1990).
111. Murrell, G. A. An insight into Dupuytren's contracture. *Ann. R. Coll. Surg. Engl.* **74**, 156–160 (1992).
112. Hindocha, S., Stanley, J. K., Watson, J. S. & Bayat, A. Revised Tubiana's staging system for assessment of disease severity in Dupuytren's disease—preliminary clinical findings. *Hand (NY)* **3**, 80–86 (2008).
113. Au-Yong, I. T., Wildin, C. J., Dias, J. J. & Page, R. E. A review of common practice in Dupuytren surgery. *Tech. Hand Up Extrem. Surg.* **9**, 178–187 (2005).
114. Shaw, R. B. Jr, Chong, A. K., Zhang, A., Hentz, V. R. & Chang, J. Dupuytren's disease: history, diagnosis, and treatment. *Plast. Reconstr. Surg.* **120**, 44e–54e (2007).
115. Hurst, L. C. *et al.* Injectable collagenase *Clostridium histolyticum* for Dupuytren's contracture. *N. Engl. J. Med.* **361**, 968–979 (2009).
116. Badalamente, M. A., Hurst, L. C. & Hentz, V. R. Collagen as a clinical target: nonoperative treatment of Dupuytren's disease. *J. Hand Surg. Am.* **27**, 788–798 (2002).
117. Seegenschmiedt, M. H., Olschewski, T. & Guntrum, F. Radiotherapy optimization in early-stage Dupuytren's contracture: first results of a randomized clinical study. *Int. J. Radiat. Oncol. Biol. Phys.* **49**, 785–798 (2001).
118. Betz, N. *et al.* Radiotherapy in early-stage Dupuytren's contracture. Long-term results after 13 years. *Strahlenther Onkol.* **186**, 82–90 (2010).
119. Pittet, B. *et al.* Effect of γ-interferon on the clinical and biologic evolution of hypertrophic scars and Dupuytren's disease: an open pilot study. *Plast. Reconstr. Surg.* **93**, 1224–1235 (1994).
120. Meek, R. M., McLellan, S., Reilly, J. & Crossan, J. F. The effect of steroids on Dupuytren's disease: role of programmed cell death. *J. Hand Surg. Br.* **27**, 270–273 (2002).
121. Rives, K., Gelberman, R., Smith, B. & Carney, K. Severe contractures of the proximal interphalangeal joint in Dupuytren's disease: results of a prospective trial of operative correction and dynamic extension splinting. *J. Hand Surg. Am.* **17**, 1153–1159 (1992).
122. Ebskov, L. B., Boeckstyns, M. E., Sorensen, A. I. & Soe-Nielsen, N. Results after surgery for severe Dupuytren's contracture: does a dynamic extension splint influence outcome? *Scand. J. Plast. Reconstr Surg. Hand Surg.* **34**, 155–160 (2000).
123. Larson, D. & Jerosch-Herold, C. Clinical effectiveness of post-operative splinting after surgical release of Dupuytren's contracture: a systematic review. *BMC Musculoskelet. Disord.* **9**, 104 (2008).
124. Brenner, P. & Rayan, G. M. *Dupuytren's Disease: a Concept of Surgical Treatment* (New York, Springer, 2003).
125. Watt, A. J., Curtin, C. M. & Hentz, V. R. Collagenase injection as nonsurgical treatment of dupuytren's disease: 8-year follow-up. *J. Hand Surg. Am.* **35**, 534.e1–539.e1 (2010).
126. Johnston, P. *et al.* A complete expression profile of matrix-degrading metalloproteinases in Dupuytren's disease. *J. Hand Surg. Am.* **32**, 343–351 (2007).

Author contributions

B. Shih and A. Bayat contributed equally to researching data for the article, discussion of content, writing and reviewing/editing of the manuscript before submission.