Collagen Changes in Dupuytren's Disease

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In: Berger A, Delbruck A, Brenner P, Hinzmann (Eds)
Dupuytren's Disease
Pathobiochemistry and Clinical Management
Springer-Verlag Berlin 1994

Introduction

The major biochemical characteristic of Dupuytren's disease (DD) is the progressive and irreversible deposition of excess fibrous collagen. This proliferation of collagen certainly impairs normal function, but in some as yet unknown way it also provides the disease with its characteristic clinical feature, flexure of the fingers.

The major questions in DD are: (1) What are the stimuli that actuate the process of collagen proliferation? (2) Can one inhibit or reverse this excess deposition of collagen? (3) What is the mechanism by which the tissue contracts?

A prerequisite of any hypothesis to account for the characteristic features of DD is knowledge of the changes taking place in the collagenous structure of the aponeurosis. It cannot be assumed that all fibrotic situations are similar nor that any particular stimulating factor produces identical effects. For example, changes of collagen type follow different paths during fibrosis of the skin and kidney in scleroderma (Black et al. 1985) and during normal and hypertrophic scarring in the dermis (Bailey et al. 1975b). Any proposed stimulating factor must produce all the changes observed to occur in the collagen in DD. In contrast to most fibrotic situations, in DD one can distinguish the early and late stages of the disease. It is therefore possible to follow, at least in part, the course of the disease, and from the early stages it should be possible to distinguish between a variety of suggested stimulating factors.

The lesion primarily involves the palmar aponeurosis, i.e., the collagenous fascia or fibrous sheet separating the flexor tendon from the overlying fibrofatty layer. In the early stages discrete highly cellular nodules form, but in the later stages few nodules are present and the characteristic feature is dense fibrotic bands or cords along the aponeurosis. These changes result in flexural contraction of one or more fingers towards the palm. Studies on the collagenous tissue have therefore concentrated on comparing the nodules and the contracture bands.

Alterations in the Collagenous Tissue

Changes in: (a) physical appearance of the fibres and their composition in terms of genetic type of collagen; (b) posttranslational modification and extracellular cross-linking and (c) the organisation of the tissues have been reported (for recent review see McFarlane et al. 1990).

Biochemical Changes

Studies on DD have attempted to identify and analyse at least three regions of the aponeurosis: (1) the highly cellular nodules, (2) the fibrous bands and (3) the apparently unaffected regions.

Composition. There is a progressive increase in the proportion of collagen in the aponeurosis from the control, at about 60%, to the bands, at about 90% and even higher in the nodules (Bazin et al. 1980; Brinkley-Parsons et al. 1981; Hamamoto et al. 1982). The amount of neutral-salt soluble and acid soluble collagen was very small, about 0.2%, from the diseased tissue compared to virtually nothing from the control. Similarly, the amount of collagen digestible by pepsin treatment increased from 80% in the controls to almost complete solubilisation for the diseased tissue, as would be expected for immature collagen.

Compositional analysis of the collagen extracted revealed a higher level of hydroxylation, increasing from five to 13 residues of hydroxylysine per 1000 residues (Brinkley-Parsons et al. 1981). This increase was accompanied by a parallel increase in the number of glycosylated hydroxylysines so that the

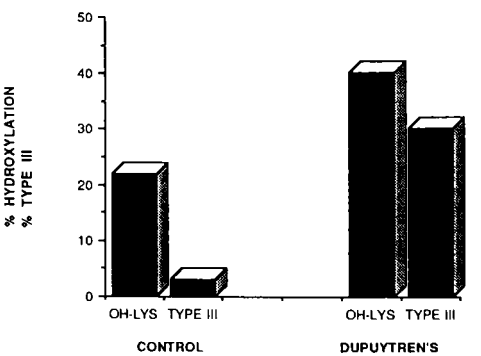

Fig. 1. Changes in the levels of hydroxylysine and type III collagen in Dupuytren's disease compared to control tissue

relative proportion of glycosylated hydroxylysines remained constant. Increased glycosylation occurred in both type I and type III collagens. The overall increase in the hydroxylation of the bands is illustrated in Fig. 1.

Collagen Types. Chemical determination of the ratio of type I to type III collagen has been carried out using either pepsin digestion, which solubilised over 90% of the collagen and therefore gave a representative sample (Bailey et al. 1977; Bazin et al. 1980; Gelberman et al. 1980), or complete dissolution of the sample by cyanogen bromide in formic acid (Brinkley-Parsons et al. 1981). Similar results were obtained for ratios of types I to III. Basically there was an increase from 1%–2% type III in the normal aponeurosis to 10%–15% in the apparently uninvolved, 10%–20% in the nodules, and 30%–40% in the fibrous bands (Fig. 1).

Murrell et al. (1989) have suggested that the change in the type I to III ratio is due to a decrease in the synthesis of type I collagen. However, this proposal is based on decreased synthesis of type I collagen from fibroblasts in high density culture and may not relate to in vivo conditions. The decrease in type I necessary to account for the apparent increase in type III from 3% to 30% would be dramatic and unlikely in a fibrotic condition.

These changes in collagen types determined by analysis of the tissue are analogous to those occurring in granulation tissue of dermal wounds (Bailey et al. 1975a) and in hypertrophic scars (Bailey et al. 1975b). One would expect the greatest amount of type III in the nodules, where there is a rapid proliferation of collagen, and decreasing amounts in the bands as they mature, if Dupuytren's contracture follows the pattern of normal wounds and fibrotic lesions. However, a large amount of type III would be retained over a long time period if the bands follow a similar course to those of the hypertrophic scar. Cross-link studies show that the DD bands do not mature, indicating more rapid turnover of collagen in the band. In addition, analysis of collagen from patients with long-standing Dupuytren's revealed biochemical changes similar to those in short-term disease (Brinkley-Parsons et al. 1981), indicating a failure to mature analogous to what occurs in the hypertrophic scar.

Other collagen types have been detected, as in granulation tissue, but in much smaller amounts. The relative proportions of type V and type I trimer were found to double from 5% to 9% and 2% to 5%, respectively. These increases are similar to those found in hypertrophic scars (Ehrlich et al. 1982). Type VI collagen (Timpl and Engel 1987) is not detectable in normal tendon, but examination of the aponeurosis of Dupuytren's revealed the presence of type VI in the fascicular sheath. Electron microscopic examination of the nodules and bands showed typical 100 nm banded fibrils, but supporting evidence that the fibrils were type VI has not yet been provided by immunofluorescent staining.

Cross-Linking. Distinct differences in the cross-link patterns were reported by Bailey and coworkers (Bailey et al. 1977; Bazin et al. 1980) and have been confirmed by others (Brinkley-Parsons et al. 1981; Gelberman et al. 1980;

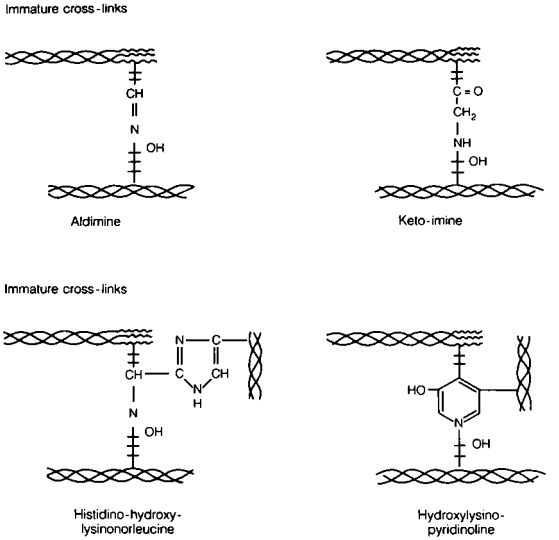

Fig. 2. *Top*, formation of the divalent reducible cross-links in developing collagen fibres. *Bottom*, further reaction of these cross-links to form the trivalent nonreducible cross-links found in mature tissues

Hanyu et al. 1984). As anticipated for mature collagen the control tissue revealed hexosyl lysines as the major reducible components, the divalent reducible cross-links being barely detectable. In contrast, the major reducible components of the nodules and the bands were the two reducible cross-links, the aldimine dehydro-hydroxylysinonorleucine and the keto-imine, hydroxylysino-keto-norleucine (Fig. 2). The reported increased levels of lysyl oxidase (Hamamoto et al. 1982) are consistent with the higher levels of these reducible cross-links. Surprisingly the apparently unaffected parts of the aponeurosis also showed increased amounts of the reducible cross-links, although a significant level of hexosyl lysines is still present. It should be remembered that the hexosyl lysines are not cross-links but can be considered good indicators of maturity (Bailey et al. 1974). Reducible cross-links are only present in immature tissues, and hexosyl lysine in mature tissue. Hanyu et al. (1984) reported equal amounts of pyridinoline in the normal and affected aponeurosis and concluded that the cross-link was not involved in the pathogenesis of the disease. Recently we have reanalysed the tissues for the non-reducible cross-links, histidino-hydroxylysinonorleucine (HHL) and pyridinoline (Fig. 2). The levels of HHL decreased by about 50% in the bands compared to the controls, as expected for an immature tissue. In contrast, a

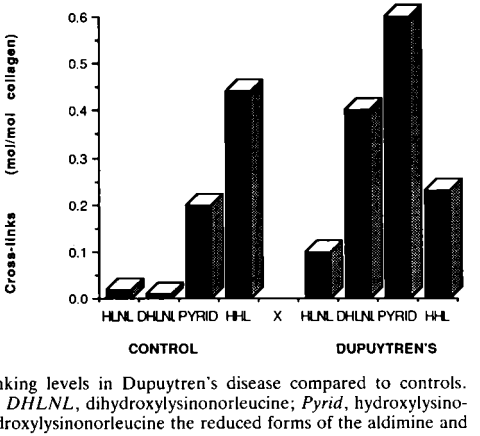

Fig. 3. Changes in the cross-linking levels in Dupuytren's disease compared to controls. *HLNL*, hydroxylysinonorleucine *DHLNL*, dihydroxylysinonorleucine; *Pyrid*, hydroxylysinopyridinoline; *HHL*, histidino-hydroxylysinonorleucine the reduced forms of the aldimine and keto-imine respectively

significant increase of about threefold in the pyridinoline levels occurred in the DD bands compared to the controls (Fig. 3). This finding is consistent with the overall increase in hydroxylation and DHLNL, rather than indicating maturity of the tissue.

The apparently unaffected aponeurosis shows clear signs of some newly synthesised collagen, whilst the highly active nodules contain completely new collagen. The bands are mainly newly synthesised collagen but contain some mature features similar to the control, i.e., increased hexosyl lysines, clearly indicating that some maturation of the tissue has occurred.

Elastic Fibres. These fibres are a two component system consisting mainly of elastin but with a small proportion of microfibrils. Analysis of the amount of elastin was determined by the cross-links desmosine and iso-desmosine and found to be decreased by about 70% in the DD bands from a level of about 1% in the controls, consistant with increased amounts of newly synthesised collagen.

Structural Changes

Briefly, histological changes in DD (Hueston 1963; Larson et al. 1960; Millesi 1965; Millesi et al. 1983; Tubiana 1967) revealed two components, a highly cellular nodule and a virtually acellular scar tissue. The nodules are characterised by a network of thin collagen fibres and proteoglycans metachromatic to toluidine blue. In contrast, the fibres of the bands are more tightly packed and more orientated in a preferred direction than those of the normal aponeurosis.

Scanning electron microscopy has revealed similar changes (Hunter and Ogdon 1975; Legge et al. 1981). Using transmission electron microscopy it is seen that the individual collagen fibers possess the normal structure and typical axial banding pattern of 67 nm. Similarly, analysis of the fibres by both wide and low angle X-ray diffraction showed no detectable difference between normal tissue and that from DD patients (Brinkley-Parsons et al. 1981).

It would appear from these results that the structure of the individual collagen fibres in DD is indistinguishable from that of normal collagen fibres. However, using indirect immunofluorescence (von der Mark 1982) it is possible to determine the distribution of the various collagen types in tissues and a different picture emerges. When the normal aponeurosis was stained with antibodies to type I collagen uniform staining occurred as expected. With types III and V the staining was limited to the periphery of the regularly arranged bundles or fascicules (Bazin et al. 1980). This can be compared to the staining of Achilles tendon, where the fibre bundles of type I were surrounded mainly by fibres of type III with some IV and V collagen (Duance et al. 1977). A similar analysis of the diseased aponeurosis failed to reveal bundles with a surrounding sheath. The nodules were intensely stained with antibodies to type III and type V fibres, which were both distributed randomly amongst the major type I fibres, and the bundles were clearly grossly disorganised. The fibrous bands revealed aligned fibres which stained for both type I and type III, but the type III fibres were randomly distributed rather than confined to the bundle sheaths as observed in the normal aponeurosis (Fig. 4). Staining of the apparently unaffected areas revealed much the same picture as for the normal aponeurosis, except that in some areas the staining of the bundle sheath was more intense.

The immunohistochemical evidence clearly suggests that it is at the higher level of order of the fibre bundles or fascicules that the structure has broken down rather than at the level of the individual fibres themselves.

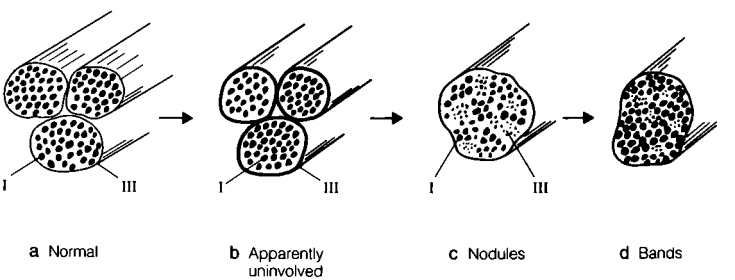

Fig. 4a–d. Development of Dupuytren's disease. **a** Normal aponeurosis: fascicular structure with type I fibres sheathed in type III collagen. **b** Apparently uninvolved: thickening of the fascicular sheath. **c** Nodules: loss of the fascicular structure and the formation of new fine fibres. **d** Bands or cords, tightly packed fibrils of type I and type III collagen but no fascicular structure

Discussion of the Biochemical and Structural Changes

The significance of the changes in collagen types in relation to DD is unknown. Excessive hydroxylation and the presence of type III collagen are typical of rapidly growing tissues with high plasticity, such as granulation tissue and embryonic tissue, rather than contracted tissues in particular. It is unlikely these changes are products solely of the myofibroblast since they are consistent in all cases compared to the sporadic appearance of the myofibroblasts themselves.

The major biochemical features of DD are similar to those of hypertrophic scar tissue in that the tissue fails to mature as in normal scars but, instead, maintains a high turnover rate.

We also observed that the disease is not strictly focal and limited to the nodules but is clearly evident in apparently unaffected parts of the aponeurosis (Bailey et al. 1979; Brinkley-Parsons et al. 1981). This is consistent with the well accepted clinical observation that DD can recur within the same aponeurosis, presumably due to failure to eliminate the disease by excision only of the grossly affected tissue. We have suggested (Bazin et al. 1980) that the disease could be initiated and/or propagated by cells migrating along the collagen bundle sheaths, that is, the equivalent in the aponeurosis of the endotendinium. The presence of myofibroblasts in the apparently unaffected aponeurosis (Bazin et al. 1980) supports this proposal, but this latter finding was not suported by Brinkley-Parsons (1981). However, Gelberman et al. (1980) have correlated recurrence of DD with those patients in whom myofibroblasts were detected.

As McGrouther (1982) and McFarlane (1974) have pointed out, the pattern of DD is not random but the nodules and tendonous bands follow anatomical pathways, that is, primarily the longitudinal fibres of the palmar fascia. This is precisely where there are lines of force passing from the palm to the fingers. Fibroblasts have long been known to be stimulated to lay down collagen along lines of force. This progression along the aponeurosis rather than specific localisation is consistent with the important finding that the apparently uninvolved part of the aponeurosis shows biochemical changes.

The aponeurosis has been shown to have a fascicular structure, the major type I fibre bundles being surrounded by a sheath of type III fibres. This structure is grossly disorganised in the highly cellular nodules and, although the fibres realign in the bands, the destroyed fascicular structure is not reformed, the type III being distributed at random. The ultrastructure studies have certainly demonstrated that the collagen fibres themselves are normal, but it is at the higher level of the fibre bundle structure of the aponeurosis that irreversible damage is seen.

Mechanism of Contraction

Several theories of contracture have been proposed, unfortunately none of which can be considered satisfactory. The early proposal, that contraction was due to the ability of collagen to shrink in vivo (Paylingwright 1954, cited in Ryan et al. 1974), can be discounted. Such shrinkage only occurs at 65°C or in strong denaturing agents and therefore cannot occur in vivo. Furthermore, it would be easy to demonstrate the presence of the denatured form of collagen, i.e., gelatin, by histological and physical techniques. However, the work did focus attention on the extracellular matrix. A further proposal suggested the fibres were shorter due to structural disorganisation (Hueston 1974) but there is little supporting evidence. In fact the fibres in the bands tend to be highly organized. More recently Legge et al. (1981) have proposed that the shorter wave form and helical twist of the fibres might account for the shortening.

In 1972 Gabbiani and Majno described the presence of the myofibroblast in DD tissue, and the emphasis switched to the cellular components. They proposed that as an active contractile cell the myofibroblast was involved in the contraction process. Since that time many investigators have confirmed the presence of these cells in the palmar fascia of DD patients. The role of these cells must involve physical connections between the cells and the collagen fibres. Although it is an attractive hypothesis which can account for contraction in all types of wounds, confirmation of their role and precise mechanism of action is still awaited.

The proliferation of collagen disrupts the normal smooth working surface of the aponeurosis and could lead to attachment to adjoining palmar fascia ligaments and possibly to the dermis. This would certainly prevent smooth movements of these ligaments in normal use of the hand, and the force exerted on flexing the fingers could lead to further proliferation of collagen at these points. Indeed, the fibrotic lesion can be seen to follow the lines of tension and look like a thickened tendon. This type of organisation would reduce extensibility of the tissue but quite why this leads to flexural contraction of the fingers rather than fibrotic swelling in the palmar fascia is ot clear. It is therefore worth considering a number of concepts and possible mechanisms of contraction.

First, a rather naive concept would be that, since the fingers' normal resting position is the relaxed 'fist' position, microadhesions could build up, slowly restricting the ability to flex the fingers; indeed, flexing would aggravate the fibrosis at just these attachment points. This hypothesis would not involve any 'contraction' of the collagenous tissue, only an inability to stretch.

Second, Glimcher and colleagues (Brinkley-Parsons et al. 1981) consider the fibres of the palmar fascia of DD to be structurally normal and that there is no folding or bunching of the fibres. They view the process of contraction as progressive replacement of the tissue fabric by a perfectly normal new piece of fabric but considerably shorter in length. However, this does not answer the question why part of the fascia is replaced by a shorter piece. The authors suggest that this can be achieved by myofibroblasts pulling the edges of the

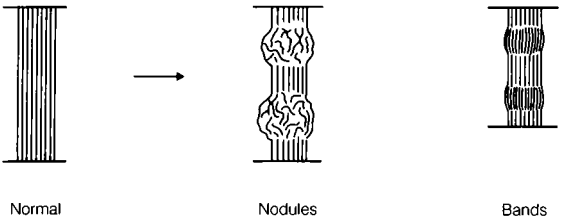

Fig. 5. Contracture of the aponeurosis. The multiple, highly cellular and grossly disorganized fibrous nodules formed in the aponeurosis contract like scar tissue to form the shorter organized fibrous bands, thus reducing the overall length of the aponeurosis. The actual mechanism of contraction is presumably through the same mechanism as scar tissue, possibly involving fibroblasts or myofibroblasts

affected tissue closer together. We are therefore back to the hypothesis that the basic mechanism is contraction of the tissue by myofibroblasts.

It is highly unlikely that contraction involves a smooth progressive renewal of the palmar fascia fibres with a structure similar to the original but considerably shorter, as proposed by Glimcher and coworkers. There is considerable disorganisation in the initial stages within the nodules and the final clinical manifestations are of thickened protruberances in the palm clearly demonstrating excessive collagenous tissue. This cannot all be laid down in the same manner as the original aponeurosis. The formation of a 'normal' aponeurosis would entail the orderly development of the fascicules bound together by type III collagenous sheaths as in normal aponeurosis. The high proportion of type III collagen suggested that this was unlikely and recent immunohistochemical studies of the bands clearly demonstrate the absence of a fasicular structure.

Third, an alternative simple theory involving contraction would then be as follows: The nodules formed along the aponeurosis contract like any wound as they progress to fibrous bands. The aponeurosis has a fixed length from the palm to the digits hence the additive effect of the contraction of multiple nodules by myofibroblasts would effectively shorten the aponeurosis which, having fixed anchorage points, would result in flexure of the fingers (Fig. 5). Further, the fibres in the bands are orientated to a greater degree than the normal aponeurosis and do not therefore possess the flexibility of the original fasicular organization.

The precise contractile mechanism is not yet clear but must involve fibroblasts or myofibroblasts contracting the nodular space (Gabbiani and Majno 1972). Fibroblasts certainly have the ability to contract fibrous collagen 'gels' and these cells are seen to possess bundles of intracellular actin filaments. It has been proposed that these filaments attach to the cell membrane through the integrins and that fibronectin acts as the extracellular adhesive between the integrins and the collagen fibres (Singer et al. 1984; Hynes 1987). The contractile ability of the cytoskeletal actin filaments remains to be elucidated.

Concluding Remarks

In our own studies we have shown that the first signs of change in DD are observed in the interfasicular connective tissue of the aponeurosis suggesting the disease is initiated in this region. Following progression from the nodules to the bands we have shown that, although the fibres are well orientated in the bands, there is no fascicular structure corresponding to the unaffected aponeurosis. Further, we have demonstrated that these changes are not unique but follow the same pattern as those occurring in wound granulation tissue and more particularly the hypertrophic scar. The inability of the collagen to mature suggests that the stimulating factor may be endogenous. Unfortunately, the reports of changes occurring when fibroblasts are grown in vitro are conflicting. Some workers report changes analogous to the in vivo observations whilst others report no differences from the controls. These differences may be due to the use of primary cultures as opposed to cells obtained after several passages.

It is of course possible that the collagen of DD patients is genetically defective and therefore responds in an abnormal way to stimuli that would not affect normal individuals. The genetic background to DD has been investigated. Welsh and Spencer (1990) concluded that it is not an HLA-linked disease but, based on the typing of patients using specific collagen type antibodies, suggested that a form of DD may indeed be an inherited disorder. If the collagen is abnormal then the change must be subtle since no biochemical difference has been reported to date.

The ultimate solution to the disease must be to identify the stimulating factor, an exogenous mediator or transformed cell which, based on the recurrence of the disease, albeit slow, appears to be retained in the tissue. A currently fashionable stimulating factor is the superoxide free radical (Halliwell and Gutteridge 1989), production of which has been invoked in the case of DD to account for the proliferation of fibroblasts (Murrell et al. 1990). However, it is not clear whether the earliest recognizable event, i.e., damage to the endothelium, is caused by free radicals or whether the damage results in ischaemia with consequent production of free radicals.

Unfortunately, in DD, fibrosis is already excessive before clinical presentation and knowledge of the stimulating factor is unlikely to help clinically at this stage. However, based on our understanding of the fundamentals of the synthesis and degradation of collagen, there are several approaches that might result in regression of the fibrosis: (1) control of the production of mRNA at the transcriptional level; (2) control of the posttranslational modification by specific inhibitors of, for example, prolyl hydroxylase, which are known to be effective in reducing synthesis; (3) controlled degradation of the collagen by selective use of collagenases and neutral proteinases. Unfortunately, at the present time inhibiting synthesis and the removal of excess collagen present formidable difficulties.

Although much has been learned about the changes of the collagen in DD, this knowledge has not yet helped our understanding of the nature of the

stimulating factor nor the fundamental mechanism of contraction. However, the recent increased understanding of the nature of collagen, its complex biosynthetic and degradative pathways, together with a more detailed biochemical analysis of the progression of the disease will surely provide answers in the very near future to these two major questions in DD.

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