

ARD

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Leader

Tendon lesions and soft tissue rheumatism—great outback or great opportunity?

In 1979, Dixon described soft tissue rheumatism as *'the great outback of Rheumatology, a vast frontier land, ill-defined and little explained, its features poorly categorised and far from internationally agreed.'* Has much changed in the past 15 years?

Soft tissue rheumatism in 1995

Musculoskeletal symptoms without frank arthritis are very common. Most of us suffer such symptoms each year. They usually occur in one region, in an individual who is otherwise well. These regional musculoskeletal disorders, which have commonly been overlooked in the planning and provision of health care, are disorders of major and increasing importance.

Soft tissue rheumatism accounts for up to 25% of all hospital consultations for the rheumatic disorders.¹ Shoulder pain is prevalent and often under reported, with symptoms or disability in at least 20% of the elderly hospital population.² Data from United Kingdom general practitioners suggest that, each year, approximately 1:170 of the adult population will present to their general practitioner with a new episode of shoulder pain.³ Lateral epicondylitis is estimated to affect four adults per 1000 each year, particularly those aged 35–54 years. Most experience a recurrence of symptoms within 18 months.⁴

Soft tissue rheumatism is certainly still confusing. In clinical practice it is often difficult to ascertain the underlying disorder. Different tissues such as muscle, ligament, tendon, and tendon sheaths can be affected, and often minor injury and inflammation cause much pain and dysfunction. Disorders can be classified by clinico-pathological process (tendinitis), by anatomical region (shoulder pain), or by aetiology (repetitive strain syndrome). The heterogeneity of soft tissue rheumatism poses considerable problems in arriving at a sensible programme of treatment and system of management. For example, more than 40 treatments have been proposed for lateral epicondylitis, reflecting the lack of consensus about how to treat this and other soft tissue conditions.⁵

Soft tissue rheumatism also remains costly; the lesions are chronic and have been estimated to result in the loss of up to 11 million working days annually.¹ Most cases of lateral epicondylitis are managed in primary care, although the condition causes considerable loss from work and industrial compensation. Labelle *et al*⁶ reported that, among industrial workers, an average of 62 days per patient is lost from work.

This group of diseases make up a high proportion of rheumatological practice in the UK, but traditionally little effort has been made to understand their underlying pathology. There are a number of reasons for this. Soft tissue lesions are not life threatening, unlike the much rarer immunological and inflammatory rheumatological diseases. Soft tissues are rarely biopsied, so samples are difficult to obtain and current animal models do not necessarily reflect the chronic degenerative lesions found in aging patients. However, while there is lack of pathological information on many of these lesions, there are usually adequate clinical features to allow identification of individual conditions.

Perhaps the biggest hindrance to progress in our understanding of soft tissue rheumatism has been a negative attitude to the affected tissues, which are still thought of as inert, homogeneous structures. This is certainly true of diseases where tendon tissues are principally involved.

Tendon diseases

The biological function of a tendon is to pull and transmit muscle power. Rupture—partial or complete—is its worst functional failure, but it may also fail by adhering within its sheath or by stenosis of the sheath. Tendon function can be impaired locally by trauma and in systemic disease, by inflammation and fibrosis, by impairment of blood supply, or by atrophy or degeneration and calcification, and sometimes, in systemic disease, by metabolic deposits.

The role of tendons is often considered to be passive, the tissue relatively inert and very much secondary to other joint structures such as bone, cartilage, and synovium—tissues which have received the greater share of attention. These misconceptions are belied by recent studies investigating human tendon lesions, that demonstrate that these tissues are metabolically active, interesting, and worthy of research.

HISTOLOGICAL STUDIES

In shoulder tendon lesions, changes occur in the appearance of human tendon collagen fibres and the distribution of tendon cells and arterioles. There is an increase in cells resembling chondrocytes and arteriole intimal hyperplasia, particularly in older specimens.⁷ Analysis of spontaneously ruptured tendons shows degenerative changes that include changes in collagen fibre size and orientation, with an

increased deposition of proteoglycan between the fibres. The tenocytes have enlarged vacuoles that can contain lipids, and sometimes cell necrosis is found. In certain cases calcium is deposited. These changes are not present in all tendons, although they can occur together in some specimens.⁸ Similar changes are found in human tendons removed at operation for rotator cuff degeneration and lateral epicondylitis.⁹ These studies have used routine histological techniques for descriptive investigations; other studies have investigated these lesions biochemically.

BIOCHEMICAL STUDIES

Biochemical studies have shown that diseased supraspinatus tendons have an increased concentration of dermatan sulphate and chondroitin sulphate and a three fold increase in hyaluronan,¹⁰ showing that a change in proteoglycan synthesis has occurred. There is also an increase in cell numbers, a reduced collagen content, possibly caused by an increase in collagen degradation, and in the majority (88%) an increased collagen type III content is present¹¹ (table). These changes are consistent with inflammation and a fibroproliferative response, presumably in an attempt to repair the tendon defect, although it is not known if this process is primary or secondary to the tendon rupture.

CELLULAR STUDIES

Normal tendons adapt to their mechanical environment and this has profound implications for tendon physiology and pathology. A highly specialised 'fibrocartilage' develops in regions of tendons exposed to compression.¹² These regions differ biochemically and structurally from tension bearing regions of tendon and have characteristics somewhere between that of classic tendon regions and articular cartilage.¹³ Although type I collagen remains the principal matrix component, the cellular activity in these compressed regions includes the synthesis of both type II collagen and aggrecan.¹⁴ These studies demonstrate that tendon cells are metabolically responsive, capable of repair, and maintain the matrix composition by a balance between anabolic and catabolic processes.¹⁵ The ability of aging tenocytes to synthesise macromolecules and to remodel and repair tendon defects is consequently of major importance in human tendon degeneration and injury, but much more needs to be known about the varied responses

of different populations of tenocytes and the factors that control tendon cell matrix metabolism (synthesis and turnover).

GROWTH FACTOR AND CYTOKINE STUDIES

Growth factors in general have anabolic effects on tissues, increasing matrix synthesis and reducing matrix breakdown. Cytokines such as interleukin-1 (IL-1) and tumour necrosis factor α often have the opposite effect, decreasing matrix synthesis and upregulating the proteinases that promote matrix breakdown.¹⁶ Recent studies have shown that tendons in vitro respond to IL-1 by altering the synthesis of matrix components and proteinases such as the matrix metalloproteinases.^{17 18} The production of excessive enzyme activity can exceed that of local inhibitors such as the tissue inhibitors of metalloproteinases and so lead to tissue collagen breakdown.^{16 19} Knowledge of the response of aging human tenocytes to cytokines would help determine the role of these factors in the pathological changes found in diseased tendons.

Tendon disease mechanism

These multidisciplinary studies suggest a common disease mechanism (figure), whereby various traumas to the tendon (for example impingement, trauma, hypoxia) induce growth factors that stimulate the tendon fibroblasts, changing the pattern of matrix synthesis. This alteration, with the deposition of tenascin²⁰ and new synthesis of glycosaminoglycan,⁸ may be a protective response to compression or shear forces. Whatever the cause, these changes are accompanied by cell rounding and an upregulation of proteinases that result in the loosening and then net loss of part of the collagen fibrillar network. In normal tendons these responses are followed by the tendon replacing this altered matrix, and a normal tendon structure reforms.

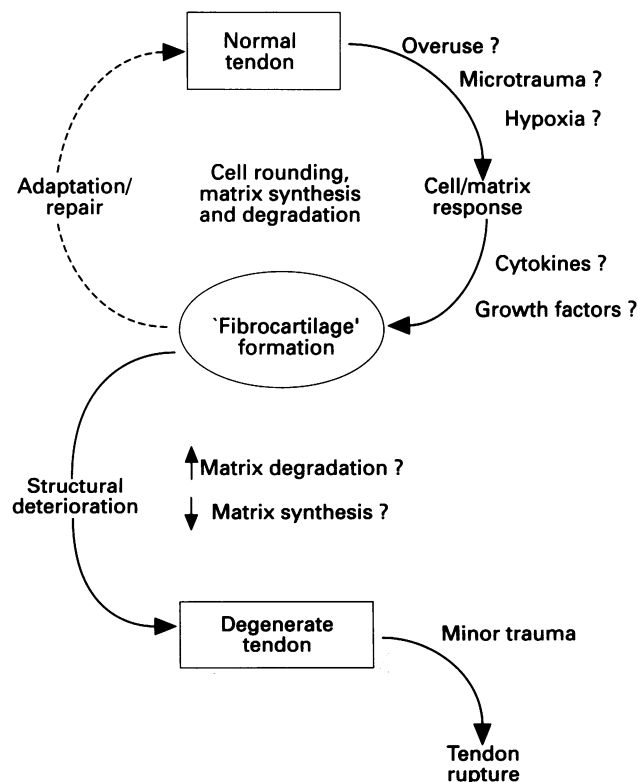
Biochemical changes in supraspinatus 'tendinitis'†

	Normal supraspinatus tendon	Degenerate supraspinatus tendon
Total collagen (μg OHP/mg dry wt)	96.3 (7.9)	83.8 (13.9)***
Type III collagen (% total collagen)	2.8 (3.2)	9.7 (5.7)***
Pepsin soluble collagen (μg OHP/mg dry wt)	1.5 (0.6)	13.1 (5.6)***
Soluble non-collagen proteins ($\mu\text{g}/\text{mg}$ dry wt)	40.9 (13.6)	91.7 (44.2)***
Sulphated glycosaminoglycans ($\mu\text{g}/\text{mg}$ dry wt)	12.3 (4.3)	13.7 (4.1)
Uronic acid ($\mu\text{g}/\text{mg}$ dry wt)	8.5 (1.9)	18.7 (3.6)***
Chondroitin sulphate ($\mu\text{g}/\text{mg}$ dry wt)	6.9 (2.6)	8.4 (2.8)*
Dermatan sulphate ($\mu\text{g}/\text{mg}$ dry wt)	2.5 (1.2)	3.8 (1.2)***
DNA ($\mu\text{g}/\text{mg}$ dry wt)	0.74 (0.3)	1.81 (1)***
Calcium ($\mu\text{g}/\text{mg}$ dry wt)	1.1 (0.35)	9/27 > 1.8‡ (range 3.3–56.7)

Values are mean (SD).

†See also references 10 and 11. OHP = Hydroxyproline.

‡33% (nine of 27) contained greater than 2 SD above the normal mean (1.8 $\mu\text{g}/\text{mg}$ dry wt); the remaining 18 specimens were within the normal range. Significant differences between groups: * $p < 0.05$; *** $p < 0.001$.



Hypothesis of tendon degeneration. Fibrocartilage formation is a key event in the process. The outcome is dependent on the ability of tenocytes to adapt and repair matrix damage

However, in some cases the tendon is unable to repair and irreversible changes in matrix composition then occur. The inappropriate and persistent synthesis of type III collagen, which was found to be increased in 17% of non-ruptured supraspinatus tendons,⁹ may substantially weaken the tendon matrix and predispose to rupture. Further degradation of the collagen may result from inappropriate action of proteinases. These changes in matrix composition are sometimes followed by the deposition of calcium salts.²¹ With these changes in composition and structure, even normal loading can cause a rupture of the tendon and subsequent loss of function.

Future prospects

Recent advances in the diagnosis and management of the more common syndromes has resulted in better understanding of and care for patients with these varied problems, and there is no good reason why they should remain 'the great outback of Rheumatology'. They do represent a *great opportunity* for detailed investigation. The careful collection of waste material from human tendon lesions should be followed by biochemical, cell biological, and molecular studies that will allow the confirmation of the proposed disease mechanisms in these metabolically active tissues and so lead to the introduction of new and effective local treatment. As knowledge of the anatomical, biochemical, physical, emotional, and behavioural mechanisms contributing to these syndromes improves, then management will become better standardised and more effective.

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