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Chronic Pain with no Identifiable Pain Generator

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Abstract

The sixteenth century French physician Ballonius, described a state of pain from muscles and joints, which he named rheumatism. Rheuma means flow, and the ideas of Ballonius were based on the theories introduced by Hippocrates, later developed by Galen, of four essential fluids in the body, sanguis, phlegm, chole and melan chole. Illness was believed to be caused by imbalances or mismatches among these fluids. Treatment consisted, among other things, of cupping and bloodletting. The concept of 'rheumatism' evolved, and physicians in the following centuries divided rheumatism into articular rheumatism and muscular rheumatism. For several hundred years and well into the nineteenth century, pain from the soft tissue of the locomotor system was generally referred to as muscular rheumatism. In the nineteenth century, hypotheses evolved concerning an inflammatory rather than fluidal pathology for both articular and muscular rheumatism.

Keywords: Fibrositis; Pathology; Soft tissue pain; Myofascial pain; Mechanism based treatments; Rheumatism

Introduction

As scientific laboratory methodology developed, the pathophysiological mechanisms underpinning articular rheumatism could successively be pinpointed and mechanism-based interventions followed. For muscular rheumatism, however, no inflammatory pathology could be detected and the general term muscular rheumatism gave way to fibrositis and later fibromyalgia during the twentieth century [1]. The latter term eventually received a definition of its own. Musculoskeletal pain is a broad descriptive term, essentially meaning pain from the locomotor system. This collective term works well for epidemiological purposes. Excluding skeletal pain from the definition, meaning the soft tissue of the locomotor system, however, the definition becomes far more vague, and epidemiological data are scarce. This is probably owing to the lack of consensus regarding the terminology for soft tissue pain, which makes epidemiological definition of cases difficult. Unlike skeletal pain, where the evolution of diagnostic tools such as X- ray and sedimentation rate have allowed for diagnoses based on pathophysiological mechanisms, soft tissue pain of the locomotor system more or less lacks diagnostic tools and depends primarily on clinical examination [2]. Diagnoses relating to locomotor soft tissue are often merely descriptive, such as myofascial pain, myalgia, tendinopathy or lumbago, and are often categorized or explained as syndromes e.g. myofascial pain syndrome, fibromyalgia syndrome, and complex regional pain syndrome. Descriptive diagnoses often become stigmatizing owing to the lack of understanding of pathophysiological mechanisms. Whereas mechanism-based diagnoses allow for treatment aimed at affecting the mechanisms of pathology, descriptive diagnoses lead to empirical treatment, also known as trial and error. Empirical treatment is often associated with strong beliefs in spite of an absence of scientific evidence. It is important that these treatments be scientifically evaluated. It is also important to develop scientific equipment that allows for mechanism-based diagnoses relating to the soft tissue of the locomotor system. Only then will it be possible to develop mechanism-based treatments for soft tissue musculoskeletal pain. Pain from tendons and tendinous muscle insertions is a subgroup of musculoskeletal pain. It is a common reason for consultations in all outpatient settings. There is very little epidemiological data on prevalence and incidence of tendon pain in general, due to a lack of consensus regarding the terminology of tendon pain in various locations and durations.

Discussion

Recently a collective term, tendinopathy, has been suggested. Common locations for tendon pain are the Achilles tendon, patellar tendon and lateral elbow. Prevalence of pain from the Achilles tendon is estimated to 7-11% of all runners. In the general population, prevalence could be estimated to about half that, based on the fact that about one third of sufferers have a more sedentary lifestyle. The incidence of tendon pain from the lateral elbow is 1-3% in the population [3]. Peak prevalence of Achilles and lateral elbow tendon pain is between 35 and 45 years of age. The cause is primarily repetitive overuse with the following bio-mechanical risk factors acknowledged in sports as well as in industrial labour: excessive duration, heavy load, poor technique, poor ergonomics and poor equipment. Other, intrinsic, risk factors are genetic variances in collagen or glycoprotein tenascin C, metabolic diseases such as diabetes, obesity, hyperthyroidism, hyperparathyroidism and rheumatologic disorders such as rheumatoid arthritis, systemic lupus erythematosus and psoriasis. Medication with fluoroquinolone antibiotics is associated with chronic tendon pain, and an association between tendon pain and statins, as well as oral contraceptives, has been proposed. The acute stage of tendon pain comprises prostaglandin mediated inflammatory processes and is accordingly termed tendinitis. During the first 24 hours, resident immune cells such as macrophages and mast cells predominate [4]. Vasoactive factors and cytokines that mediate vascular leakage and migration of leucocytes, primarily neutrophils, towards the inflammatory site are released. Prostaglandins and leukotrienes are produced and activation of the complement system occurs, as well as excitation and sensitization of sensory nerves, peripheral as well as central. The inflammatory phase is followed by a proliferation phase, when resident fibroblasts increase their production of

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collagen. Degradation of tissue, primarily by enzymes such as matrix metalloproteinase, is also increased, resulting in an overall increase of matrix turnover. The overall tissue turnover favours anabolic processes resulting in overall increase of tendon tissue and increased mechanical strength. The proliferation phase is followed by maturation and remodelling of the tendon tissue, which can take months or up to a year. During this time, crosslinking among collagen fibres is increased and tensile strength, elasticity and the structure of the tendon are all modified. These are the normal physiological stages of tendon repair as studied in experimental animal research. Many of these processes have also been confirmed in humans. Tendon pain often persists or recurs beyond the normal time for healing. Up to 20% of lateral elbow cases may persist after one year. In this, chronic stage, histological samples show very few inflammatory changes but instead patches of degenerative tissue consisting of calcification, mucoid tissue, lipids, fibrocartilage and disruption of the normally homogenous alignment of collagen [5]. Increased numbers of nerves and capillaries have also been noted. Hence, it has been suggested that this stage of tendon pain should be referred to as tendinosis. In clinical practice, however, it has been common not to distinguish between the acute and chronic stages of tendon pain. Thus treatment has generally been aimed at reducing acute, prostaglandin mediated inflammation in both the acute and the chronic stage of tendon pain. Treatment as suggested in the literature consists of rest, NSAIDs, and local injections of steroids. In fact, there is now convincing evidence that local injection of steroids only provides temporary pain relief and actually worsens clinical outcome in the long term. The extracellular matrix of tendinosis tendons clearly differs from that of normal tendons. The normal tendon consists of connective tissue dominated by symmetrically organized collagen, water, proteoglycans and glycol-proteins. The collagen and the proteins are produced by fibroblasts interspersed in the tissue [6]. The normal tendon can withstand considerable tensile force and its strength is reinforced by intra-molecular and intermolecular crosslinks. In tendinosis the collagen orientation is irregular, interspersed with calcifications, cartilage, fibrosis, hyper-vascularization and increased innervation. The proportion of collagen type I decreases, in favour of the less durable collagen type III. The fibroblasts of the normal tendon respond to stretching and deformation, known as mechano-transduction, with increased collagen turnover consisting of simultaneous synthesis and degradation, accompanied by release of tissue growth factors such as IGF-I, TGF-β and FGF along with inflammatory mediators such as prostaglandins, bradykinin, adenosine, IL-6 and IL-1β [7]. The increased matrix turnover results in a net synthesis of collagen in response to loading. This increase in tissue quantity and quality improves tissue strength and force transmission. In contrast, decreased levels of matrix metalloproteinase such as MMP-3, impair the matrix turnover in tendinosis. The tendinosis tissue also seems to respond to loading with exaggerated production of prostaglandins. In addition, there are reports in tendinosis of increased levels of neuropeptides such as glutamate, substance P, along with NMDA and neurokinin 1 receptors in the affected tissue, which may be part of peripheral sensitization. The fibroblasts in tendons are supported by a pool of tendon stem cells that differentiate into fibroblasts in response to stretching or deformation. Interestingly, over-stretch of TSC and high levels of prostaglandin E2 both result in differentiation of TSC into bone, fat and cartilage cells rather than fibroblasts. This may be part of the pathophysiological explanation for the degenerative findings in tendinosis. An acute inflammatory process attracts angiogenesis along with nerve sprouting related to release of growth factors such as vascular endothelial growth factor which, in the normal healing process, subsides over time. A halted inflammatory process, as suggested by the impaired matrix turnover hypothesis, may explain why the tendinosis-affected tendon contains elements of hyper-vascularity and hyper-innervation. Sensitization of the peripheral nerves leads not only to increased excitability but also to endogenous production and subsequent release of neuro-transmitters such as substance P, neurokinin A and calcitonin gene related peptide [8]. Peripheral C-nociceptors may be sub-grouped into pep- tidergic and non-eptidergic. The peptidergic nociceptors primarily use substance P and CGRP as signalling molecules, whereas the non-peptidergic nociceptors primarily use glutamate. Substance P is an eleven amino acid long polypeptide which, along with NKA, belongs to a group of mammalian peptides called tachykinins. Most of the substance P will be released by the peripheral end of the peptidergic nociceptors, where it stimulates the inflammatory cascade. The primary receptor for substance P is the NK1 receptor. It is widely distributed in the central nervous system but has also been identified on or in immunologic cells, fibroblasts, tenocytes, endothelial cells, synovial cells, keratinocytes and osteoclasts. New substance P-like peptides have been identified in non-neural cells from immune, endothelial and placenta tissue [9]. They, too, seem to act on the NK1 receptor, which makes the cellular interaction even more intricate. NK1 receptor mRNA increases significantly, in the dorsal horn as well as in peripheral tissue, in response to peripherally induced inflammation [10].

Conclusion

Studies clearly demonstrate that disease management protocols emphasizing tight control result in lower disease activity, more patients in remission, and less joint damage. Initiation of therapy and achieving low disease activity early in the first year of disease has a major effect on clinical and radiographic outcomes years later. Finally, initiating aggressive treatment after onset of rheumatoid arthritis and maintaining tight control is a feasible real world strategy.

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Conflict of Interest

None

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