

Tendinopathy

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Abstract Chronic tendon injuries are a common cause of pain and of restriction of sports or daily life. Even though a number of published studies have focused on tendon injuries, healing and treatment, the pathogenesis still remains enigmatic. The pathogenesis of chronic tendon injuries is considered multifactorial, however the precise role of each predisposing factor remains incompletely understood. The association between tendinopathy and pain should also be clarified, as the presence of tendinopathic lesions does not always lead to symptoms, but they are the necessary pre-existing conditions for spontaneous tendon ruptures. In this article, the histological features, the

pathogenetic theories of tendinopathy, and the possible sources of pain are reviewed.

Keywords Tendinopathy · Tendon injury · Tendon healing · Ruptures · Musculoskeletal rehabilitation · Physical medicine and rehabilitation · Review

Introduction

Tendon is a crucial component of the musculoskeletal system. Tendons connect muscle to bone and transmit forces to produce movements. Tendon pathologies may be acute or chronic. Chronic tendon injury, or tendinopathy, characterized by pain, focal tendon tenderness, and impaired performance. The pathogenesis of tendinopathy is poorly understood, and it has been variously defined as a degenerative condition or as a failure of the healing process [1]. Moreover, the role of inflammation in tendinopathy is not clearly established and is a matter of debate.

Tendon injury can affect people of all ages, and can impair the activity of young and old adults in their work environment or sports activities. The exact incidence of tendinopathy in the general population is difficult to assess, but it is estimated that approximately 30 % of general practice consultations for musculoskeletal pain are related to tendon problems [2]. The AAOS estimates that almost 2,000,000 people consulted a physician because of a rotator cuff problem in 2008 [3]. Tendinopathies are common in young and active patients. For example, more Achilles tendon injuries have been reported in runners compared to age-matched control, and the incidence in top-level runners has been estimated between 7 and 9 % [4]. However, the condition is by no means confined to athletes, as 30 % of Achilles tendinopathy patients have a sedentary lifestyle.

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Histological Findings

Tendinopathy can be identified by the following histological characteristics: collagen fibril disorganization, increased proteoglycan and glycosaminoglycan content, and increased noncollagenous extracellular matrix (ECM), hypercellularity, and neovascularization. These cellular and molecular changes modify the mechanical properties of tendon. At light microscopy, tendinopathy shows changes in collagen among tenocytes and also within the matrix or ground substance. Some collagen fibers separate and lose their parallel orientation, with a decrease in fiber diameter and in overall density of collagen. Collagen microtears also occur, and these may be surrounded by erythrocytes, fibrin, and fibronectin deposits. Within collagen fibers there are unequal and irregular crimping, loosening, and increased waviness, in contrast to the normal tight, parallel, bundled appearance. There is an increase in type III (reparative) collagen. Special stains demonstrate increase in mucoid ground substance (proteoglycans). There is much variation in cellular density in tendinopathy. In some areas, tenocytes are abnormally plentiful, with rounded nuclei and ultrastructural evidence of increased production of proteoglycan and protein, which gives them a chondroid appearance. A characteristic feature of tendinopathy is proliferation of capillaries and arterioles [5].

Pathogenesis

The pathogenesis of tendinopathy is poorly understood, and has been variously defined as a degenerative condition or as a failure of the healing process [6, 7]. The exact relationship between tendinopathy and tendon rupture remains unknown. However, tendinopathy could lead to tendon rupture. Chronic tendon injuries are facilitated by many extrinsic and intrinsic factors (Table 1). The main recognized extrinsic factor for tendon injury is repetitive or abnormal loading on tendons. Increased frequency and duration of training, changes in training pattern, poor technique, previous injuries, and environmental factors

Table 1 Intrinsic and extrinsic risk factors for tendinopathy

Intrinsic risk factors	Extrinsic risk factors
Malalignment (i.e., excessive pronation, femoral neck anteversion, etc.)	Training errors (i.e., distance, intensity, hill work, technique, fatigue, etc.)
Limb length discrepancy	Training surfaces
Muscular imbalance	Footwear and equipment
Muscular insufficiency	Environmental conditions
Metabolic disorders	Repetitive motion
Genetics	Immobilization

such as training on hard, slippery, or slanting surfaces have all been associated with tendon injuries. However, a retrospective study showed that tendinopathy was not necessarily associated with the level of physical activity [4, 8].

Tendon Extracellular Matrix and Tendinopathy

Extracellular matrix (ECM) is very important for the homeostasis of connective tissue. ECM is the substrate to which cells adhere, migrate, and differentiate. ECM imparts information to cells and tissues by providing cell-binding motifs in its own proteins or by presenting growth factors and morphogens to the cells. Physiologic and pathologic modifications of the ECM seem the most important intrinsic factors involved in tendinopathies and tendons ruptures. The turnover of ECM in normal tendon is also mediated by matrix metalloproteinases (MMPs), such as collagenases and stromelysins. They are able to denature type I collagen. The turnover of ECM is mediated by the activity of MMP-1, MMP-2, and MMP-3. After tendon rupture, the activity of MMP-1 increases, while a reduction of MMP-2 and MMP-3 has been shown. An increase in MMP-1 activity and degradation of the collagen fibril network is a potential cause of the weakening of the tendon matrix and may contribute to a mechanically less stable tendon that is susceptible to rupture. These findings may represent a failure of the normal matrix remodeling process. Tendinopathy is an active, cell-mediated process that may result from a failure to regulate specific MMP activities in response to repeated injury or mechanical strain [9].

Transglutaminase

Transglutaminase (TGs) enzymes and proteins crosslinking have long been implicated in the formation of hard tissue development, matrix maturation, and mineralization. Nine different TGs have been found in mammals. TG2, also known as tissue TGs, is widely distributed within many connective tissues, and it has been implicated in organogenesis, tissue repair, and in tissue stabilization. Injured supraspinatus tendons showed a reduction of the expression of TG2, both at the mRNA and protein levels. TGs are important in maintaining the structural integrity of tendons, thanks to their mechanical or crosslinking function under normal conditions, and a fall of TG2 may be a sign of exhaustion of the reparative capabilities of a tendon [9].

Obesity and Hypercholesterolemia

Evidence for a chronic, low-grade inflammatory state in obesity is represented principally by marked increases in plasma levels of proinflammatory cytokines such as tumor necrosis factor (TNF) and interleukin (IL)-6, and

proinflammatory chemokines such as monocyte chemoattractant protein (MCP)-1. Macrophages and other immune cells are also derived from adipose tissue, and an intricate relationship exists between them and the adipocyte-derived proinflammatory cytokines. In particular, MCP-I induces macrophage infiltration of adipose tissue. In turn, activated macrophages release additional proinflammatory cytokines: notably, the expression of TNF- α is significantly increased. This reduces the expression of adiponectin, an adipocyte-derived anti-inflammatory hormone. This altered balance between chemotactic mediators and macrophages that results in a state of persistent local inflammation [10].

Often hypercholesterolemia coexists with obesity. The detrimental effects of hypercholesterolemia on cardiovascular health are well-documented, but the effects on the musculoskeletal system, and more specifically on tendons, have not been thoroughly examined. In rats, biomechanical testing revealed a significant reduction in normalized stiffness in hypercholesterolemic rats compared with controls 4 weeks after injury, whereas histologic analyses showed no significant differences in collagen organization, cellularity, or cell shape between groups [11••].

Hyperglycemia

Diabetes Mellitus has been associated with compromised tissue function, increased susceptibility to tendon injury, and reduced healing capacity [12••]. This is at least partially a consequence of collagen crosslinking by advanced glycation end products (AGEs). These complex molecules can alter the mechanical properties of connective tissue as they cross-link with collagen fibers [12••]. In tendons, AGE formation affects the interactions between collagen fibers, ECM protein, and tenocytes. These changes have been associated with both reduced healing capacity and altered mechanical properties of connective tissues. The formation of AGEs changes the way in which tendons react to loading, by reducing the sliding of collagen fibers [13]. On the other hand, tendons try to compensate for this loss of function by increasing collagen fiber stretch, which may have potentially important implications for predisposing collagen fibrils to damage during everyday use. Tissue stiffness does not appear to be significantly affected. Therefore, physiological loads in aged and diabetic tendons could involve fiber “over-stretching”, with accelerated accumulation of damage [13].

Estrogens and Insulin-Like Growth Factor-1 (IGF-1)

Gender differences in the physical and mechanical properties of tendons should also be considered [14]. A bimodal

distribution of age at the time of Achilles tendon rupture has been noted.

In men, peak incidence rate occurs in the fourth decade, whereas in women, the risk of Achilles tendon rupture increase after the fifth decade [15]. Women seem to have a greater risk of tendon injuries compared to men. However, there is no monofactorial explanation for this sex disparity. Many factors are involved in this phenomenon, including anatomical differences and sex differences in hormonal levels. A morphological study compared Achilles and patellar tendons in trained and untrained people [16]. The ability of Achilles and patellar tendons to adapt to loading was different between genders. In fact, the Achilles and patellar tendon cross-sectional area was greater in trained people compared to untrained people in response to mechanical loading, but in trained men the increase was greater than in trained women. Compared to men, women have an attenuated tendon response to training, a lower tendon collagen synthesis rate following acute exercise, and a rate of tendon collagen synthesis which is further attenuated with elevated estradiol levels. At histology, collagen synthesis in response to exercise was lower in women [16]. Tendon collagen synthesis was still elevated in men 72 h after exercise, whereas in women no difference in tendon collagen synthesis was observed between the leg which had performed exercise and the control resting leg.

Tenocytes from ovariectomized and old rats showed a significantly lower proliferation rate, a decreased synthesis of collagen type I, and overexpression of MMPs compared to young controls: aging and, more significantly, estrogen levels may affect tendon metabolism and healing [17]. Oral contraceptives (OC) affect, directly or indirectly, the tendon collagen synthesis. Women who are chronically exposed to high levels of estrogen, for example users of OC, may have an altered collagen content of tendons and ligaments, which may change the biomechanical properties [18]. In fact, lower collagen synthesis has been observed in exercising women versus men, and in the users of OC versus nonusers [19]. Endogenous or exogenous estrogen may influence the risk of injuries by changing the structural composition of ligaments and tendons. However, data are equivocal. Animal studies have reported no effect of estrogen on the mechanical properties of sheep knee ligaments, whereas a study on rabbits detected a lower failure load of ACL after 30 days of estrogen administration [20, 21]. The effects of corticosteroid hormones on tendons seem to be different between young and older post-menopausal women. While in younger women stimulation by estrogens seems to have detrimental effects on tendons, in older post-menopausal women they seem to have stimulating effects. In fact,

tendon collagen fractional synthesis rate is reduced in young oral contraceptive users compared with controls.

Growth hormone (GH) and insulin-like growth factor-I (IGF-I) are also important hormones, as they stimulate collagen synthesis in connective tissue. An animal study showed that IGF-1 is involved in mediating the effects of estrogen on tendons and muscle [17]. IGF-1 exerts an important role in modulating the synthesis of tendon collagen proteins. Studies in humans with pathologically high levels of GH/IGF-I, and in healthy humans who receive either weeks of GH administration or acute injection of IGF-I into connective tissue, demonstrate increased expression and synthesis of collagen in muscle and tendon [22]. The GH/IGF-I axis is able to influence both morphology and mRNA levels of selected genes in the muscle-tendon unit of mice [23].

Thyroid Hormones and Tendons

The relationship between thyroid disorders and shoulder pain has been suspected since the late 1920s [24]. More recently, such association has been more formally hypothesized, and thyroid diseases have been linked to idiopathic tendinopathies. Thyroid hormones (THs) play an essential role in the development and metabolism of many tissues. Their effects occur mainly through T3 (Triiodothyronine), which regulates gene expression by binding to the TH receptors (TRs)-a and -b. T4 (Thyroxine) is important for both collagen synthesis and ECM homeostasis. Epidemiological studies reported that patients with rotator cuff tear and associated thyroid disorders present earlier onset of symptoms, longer natural history, and they undergo surgery more frequently compared to a control population. In particular, of 440 patients operated for a rotator cuff tear, nearly 60 % reported a thyroid disorder [25••].

The presence of THs nuclear receptors on human tenocytes has recently been demonstrated. In vitro, THs induced tenocytes growth, reduced the doubling time, and counteracted apoptosis in healthy tenocyte isolated from rotator cuff tendons in a dose- and time-dependent manner [26••].

The relationship between THs and collagen disorders has been speculated, but only recently the association between THs and tenocyte ECM protein secretion has been shown. In an in vitro study, tenocytes were cultivated in the presence of T3 and T4, and with the addition of ascorbic acid [27]. The synthesis of collagen I was increased by the presence of THs, while the synthesis of collagen III was not affected by the presence of THs. This is interesting because, although collagen III increased during the early remodeling phase and in tendinopathies, the lack of collagen III indicates that the tendons are healthy. This study

also found an increased synthesis of non-collagen proteins in the presence of THs and ascorbic acid, including biglycan and COMP. Biglycan is a small leucine-rich protein, which is present in the tendon during healing, and activates remodeling. COMP is a protein present in many musculoskeletal tissues, including tendons, ligaments, and menisci. Its function is not well understood, and it may regulate cell migration and attachment, as well as cell proliferation and apoptosis. These findings show the important role of THs on the homeostasis of tendons, acting directly on tenocytes by stimulating their proliferation, counteracting apoptosis, and regulating the synthesis of ECM proteins.

The Role of Genetics

In addition to intrinsic and extrinsic factors, genetics could play a role in the pathogenesis of tendinopathy. An underlying genetic factor as a contributing cause to tendon injury was originally proposed because of an association between the ABO blood group and the incidence of Achilles tendon ruptures or chronic Achilles tendinopathy evident in Hungarian and Finnish populations with blood group O [28]. These studies implied that ABO or closely linked genes on the tip of the long arm of chromosome could be associated with tendinopathy or tendon injuries. Studies in other populations, however, did not confirm this association. A genetic component has been implicated in tendinopathies involving the Achilles tendon and the rotator cuff tendons. Polymorphisms within the COL5A1 and tenascin-C (TNC) genes have been associated with Achilles tendon injuries in a physically active population. The ABO gene on chromosome 9q34 encodes for transferases, which, apart from determining the structure of glycoprotein antigens on red blood cells, may also determine the structure of some proteins of the ECM of tendons. Individuals with the A2 allele of the COL5A1 gene are less likely to develop Achilles tendinopathy. COL1A1 and COL3A1 genes also show variable levels of expression in normal tendons and significantly increased levels of expression in painful tendinopathy. TNC, an ECM glycoprotein found in tendons, is closely linked to the ABO gene on chromosome 9q32-q34.1. The TNC gene is expressed in the myotendinous and osteotendinous junctions and is regulated by mechanical loading in a dose-dependent manner. This genetic link could also explain why there is an increased risk of contralateral rupture of the Achilles tendon in subjects with a previous rupture. COL5A1 and TNC genes may be good markers of tendinopathy, but their exact roles in the pathogenesis of the condition require further investigation. Other, as yet unidentified, genes may contribute to the pathogenesis of tendinopathy. It would seem appropriate to begin the

search for such genes by studying those encoding for the constituents of tendon such as collagens type I, III, V, XI, XII, and XIV; elastin; fibronectin; decorin; lumican; and fibromodulin [28, 29].

An Unified Pathogenic Theory for Tendinopathy

Tendinopathy is currently considered multifactorial, and the interactions of tendon overuse, unfavorable mechanical environment, and intrinsic factors would be the starting point of the pathological process. Based on these points, the pathogenesis of tendinopathy can be perceived as a 3-stage process: injury, failed healing, and clinical presentation [30]. In the first stage, tendon pain and mechanical weakness are not significant and it is possible for the tendon injury to heal spontaneously. In the second stage, the normal healing processes are diverted to an abnormal pathway, probably a consequence of unfavorable mechanical environment, disturbances of local inflammatory responses, oxidative stress, or pharmacological influences. Since the process of tendon healing involves many sequential events, including inflammation, neovascularization, neural modulations, recruitment of healing cells, proliferation, apoptosis, matrix synthesis, tenogenic differentiation and matrix remodeling, disturbances may occur at different stages [31]. The exact causes for failed healing are still poorly understood: unfavorable mechanical environment, genetic predisposition, hormonal background, and exposure to deleterious pharmacological agents may affect the healing process. In the second phase, the histopathological features of tendinopathy is shown. However, patients can remain asymptomatic until a spontaneous tendon rupture. In the third stage, the tendons became symptomatic. In this phase, spontaneous ruptures may occur, the result of mechanical weakness under normal activities [32]. Finally, when tendons become painful, non-steroidal anti-inflammatory drugs are often prescribed to relieve symptoms and resolve “inflammation”, but they may further modify the pathways of the failed healing process.

The Origin of Pain

The source of pain associated with tendinopathy has not been clarified yet. Classically, pain in tendinopathy was attributed to inflammation. However, chronically painful Achilles and patellar tendons show no evidence of inflammation, and many tendons with intratendinous lesions detected on magnetic resonance imaging or ultrasound are not painful. Pain may originate from a combination of mechanical and biochemical factors. Recent

research identified the peripheral and central pain processing pathways as an important factor in the pathogenesis of painful human tendinopathy and changes in the peripheral neuronal phenotype may be the primary source of pain. Ectopic neural ingrowth has been clearly shown in some painful conditions, such as osteoarthritis, degenerative spinal disease, and rotator cuff tears. Chronically painful tendons present ingrowth of new nerve fibers accompanying the peritendinous neovascularisation from the paratenon into the tendon proper [33]. Also, Alfredson and colleagues demonstrated an increased neuronal ingrowth. A systematic review showed that the peripheral neuronal phenotype is altered in tendinopathy. The authors found strong evidence of upregulation of the glutaminergic system in painful human tendinopathy and weaker, but still suggestive, evidence that changes in the peripheral neuronal phenotype were related to variations in pain symptomatology among patients [34].

The synthesis and release of glutamate and substance P has been also studied. Glutamate is a key metabolite and neurotransmitter involved in the transmission of pain, and it is increased in several painful musculoskeletal disorders. Glutamate NMDAR1 receptors have been frequently noted in morphologically altered tenocytes and in the peritendinous connective tissue. Substance P functions as a neurotransmitter and neuromodulator which is implicated in pain generation in animal models and human disease, and there is also some evidence for upregulation of the substance P/CGRP system in pathological tendons [34, 35].

Conclusion

Tendon injuries produce substantial morbidity and the current understanding of the mechanisms involved in tendon injury and repair is limited. Tendinopathy is currently considered a multifactorial condition. However, the precise role that each predisposing factor plays is still to be understood.

A better understanding of pathogenic mechanism and tendon healing will allow specific treatment strategies to be developed.

Compliance with Ethics Guidelines

Conflict of Interest Alessio Giai Via, Gabriele Papa, Francesco Oliva, and Nicola Maffulli declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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