

# Tendinopathy – a disease of tendons

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## SUMMARY

Tendinopathy is a common pathology of tendons and a complex medical problem. The etiology of tendinopathy is multifactorial and based on three main theories. Tendons play various roles in the human body, and their structure guarantees specific biomechanical properties. Continuous remodeling of extra-cellular matrix provides maintenance of the adequate inner composition. Damage to the structure entails disruption of homeostasis and leads to the degenerative process because of poor tendon's healing properties. The degenerative process usually passes into a chronic tendon disorder. Chronic tendinopathy is difficult to manage; it is often an underestimated and painful problem of the general population.

In this paper, we described current views on terminology, etiology and pathology of tendinopathy, focusing on the neovascularization process and its consequences.

**Keywords:** tendon, tendinopathy, neovascularization, collagen

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**Word count:** 2202 **Tables:** 1 **Figures:** 3 **References:** 57

**Received:** 15.08.2016

**Accepted:** 06.09.2016

**Published:** 30.09.2016

## TENDINITIS, TENDINOSIS OR TENDINOPATHY?

There are three main terms used commonly and alternatively to describe tendon disorders, which might cause confusion. *Tendinitis* is a historical term describing painful disease of tendons, based on the inflammatory model. This term insinuates that inflammation is the core of the pathological process [1,2,3]. Despite its historical character, the term *tendinitis* is still commonly and widely used. Recent studies have shown that inflammation is present in the initial phase of tendinopathy, but does not play as important role as it used to be believed [2,3]. Another term – *tendinosis*, refers to the degenerative process, excluding the inflammation element. It is described as a degenerative state of the tendon tissue [1,3,4,5,6]. Finally, the term *tendinopathy* describes a chronic disorder of tendons, the etiology of which is not clear [3]. It comprises the inflammatory component, but the prevailing part represents the degenerative process [7]. Animal tests have shown that acute inflammation is present at the onset of the pathology. Unfortunately, human studies in the initial phase of tendinopathy are limited [7,8,9]. Tendinopathy is a widely accepted term, describing the pathology of tendons and leaving behind the inflammatory model [7,10]. The degenerative model of tendinopathy is presently widely accepted and recognized [11]. Nowadays, it is the most proper definition for chronic tendon pathology [6,7]. The current model and approach to tendon pathology allowed to abandon anti-inflammatory methods of treatment e.g. NSAIDs (non-steroidal anti-inflammatory drugs) and corticosteroids, and lead to new methods of therapy such as platelet rich plasma and stem cell therapy [2,11].

Tendinopathy in at least one localization is very common, not only among athletes, but also in the general population [7,12].

## HOW TO EXPLAIN ETIOLOGY – UNITE THREE THEORIES

The main known hypotheses describing the origin of tendinopathy are: vascular, mechanical and neural theories. Primary risk factors of tendinopathy are presented in Table 1.

### The mechanical theory

A tendon is designed to adapt to a new load. Its intrinsic construction shows hierarchy – from collagen molecules, fibrils and fibers up to bundles of fibers and finally fascicles [13,14]. The structure of tendons has been analyzed and described by numerous authors [14,15,16,17, 18,19,20,21]. Tendons perform various important tasks in the human body like: joint stabilization, attaching muscles to bones, energy absorption and the main role – weight bearing [12,14]. The hierarchical structure and crimping pattern of collagen fibers work as a safeguard mechanism, protecting from damage in case of overload [19]. Fiber crimps create a kind of a mechanical buffer and energy absorber [7]. Every strain of the tendon tissue, in the physiological range, causes straightening of the crimps and temporary deformation. Stress, which exceeds the physiological capabilities of the tissue, will result in rupture and tear of the fibers [7,10].

Physiological activity results in increased turnover of the matrix and collagen synthesis.

Regular activity leads to the development of the tendon’s structure and upgrade of tissue resistance. Studies on animal models have shown positive influence of training on collagen turnover, increased synthesis of type I collagen and enlargement of the tendon diameter [22]. Other *in vivo* animal tests have shown, that cycling loading of the subjects caused tendon microtears [23,24]. Other authors observed that immobilization results in low enzyme activity and decreased collagen synthesis [25].

The mechanical theory is based on repetitive microtrauma of the tendon and is known in literature as an „overuse pathology” [26]. Tendons are fibro-elastic structures, physiologically adapted to maximum load that will cause 4% of its length deformation (recent reports suggest the value of 6% to even 8% of deformation) [3,27]. Mechanical stretching in the range between 0–4% of the tendon’s length ensures differentiation of tendon stem cells into tenocytes. Multipotent stem cells are able to transform into different lineages [28]. The promotion into the tenocyte lineage is characterized by increased level of type I collagen gene expression. Mechanical stimulation of tendons in physiological range of 0–4% allows obtaining new tenocytes and maintains proper structure of the tendon. Every strain over the physiological value of 4% results in the formation of microtears in the collagen structure. Stretching of more than 8% of the tendon’s length causes

**Tab. 1.** Factors involved in the development of a tendinopathy process [3,12,13].

Genetic e.g. sequence variation within the V type of collagen and tenascin C genes, blood group 0
Endocrine diseases e.g. diabetes mellitus, thyroid disorders
Rheumatologic diseases e.g. rheumatoid arthritis, gout, reactive arthritis
Inherited diseases e.g. Marfan syndrome, Ehlers-Danlos syndrome, hemochromatosis
Age
Nutrition
Body weight
Athletes
Training errors
Occupation
Equipment e.g. inappropriate shoes
Environment
Hyperthermia
Fluoroquinolone antibiotics
Corticosteroids
Joints instability
Malalignment of the lower limbs
Bony impingements

differentiation of stem cells into adipogenic, chondrogenic and osteogenic lineages [28,29]. Repetitive trauma leads to devastation of the inner structure. The local cell population is not able to properly repair extra-cellular matrix. Tendons become vulnerable to secondary injuries, and with every successive trauma, injuries accumulate. Biomechanical properties of the scar tissue are impaired as a result of degenerative changes [6].

### The vascular theory

Tendons are metabolically active tissues and, as other tissues, they require blood supply [27]. Tendons are characterized by low vascular perfusion. Critical zones with insufficient vascular supply occur in specific tendons [10,31,32, 33]. It is thought that gradual degradation of tendons is associated with hypovascular regions which expose tendons to reduced blood perfusion and tissue hypoxia. Further considerations about neovascularization and its role are described below.

### The neural theory

Tendons are innervated tissue [7]. Nerve fibers originate from surrounding muscles and dermal nerves. Four types of nerve endings are normally identified in tendons: the Ruffini corpuscles, free nerve endings, Pacini corpuscles, mainly at the tendon site, and the Golgi tendon organs, mainly at the muscle site [27,34]. Nerve endings secrete local mediators, known as neurotransmitters: substance P and CGRP (calcitonin gene related peptide) [35]. Neurotransmitters lead to mast cell degranulation and release of enzymes, chemotactic factors and growth factors, which are a group of biologically active substances that modulate the matrix turnover.

Substance P and CGRP released from nerve endings induce neurogenic inflammation [3, 33,36]. Neurotransmitters are involved in development of painful disorders in tendinopathy [33]. Substance P, CGRP, MMP 2 (metalloproteinase type 2), MMP 9 (metalloproteinase type 9), VEGF (vascular endothelial growth factor), IL 1 (interleukin type 1), IL 6 (interleukin type 6) and TNF- $\alpha$  (tumor necrosis factor  $\alpha$ ) stimulate nociceptors [37,38,39]. The above mentioned substances have been found in increased numbers among tendons affected by tendinopathy. Neural tissue ingrowth accompanies the process of neovascularization in the pathological connective tissue and is associated with the development of painful conditions.

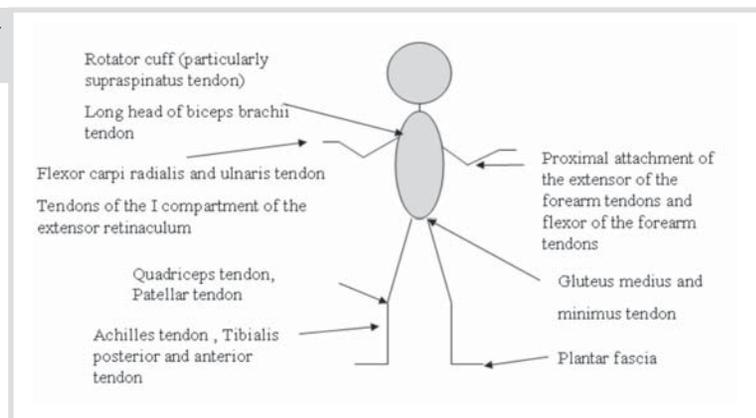
## PATHOLOGY OF TENDINOPATHY

Certain tendons during activity are more vulnerable to injuries and exposed to greater cyclic stress, also with additional compressing forces (Figure 1) [32,33,34,40,41]. Hypovascular regions are not without significance [10,30,31, 32,33]. In the degenerative process, a tendon becomes yellow, grey or brown [40]. The structure is disorganized and amorphous, softer and flattened, but on the other hand, thickening may also occur – nodular, fusiform or distracted [43].

We cannot clearly identify the onset of tendinopathy, but when it starts, it does progress [13]. Injured tendons are characterized by inferior healing, and this is the main risk factor for secondary trauma. Impaired regeneration leads to the degenerative process (Figure 2).

Tendon is not a static tissue, therefore extracellular matrix is modified all the time, adapting to a new load by resident tenocytes. Intensive matrix remodeling is a common phenomenon

**Fig. 1.** Common area of tendinopathy [13,36,42]

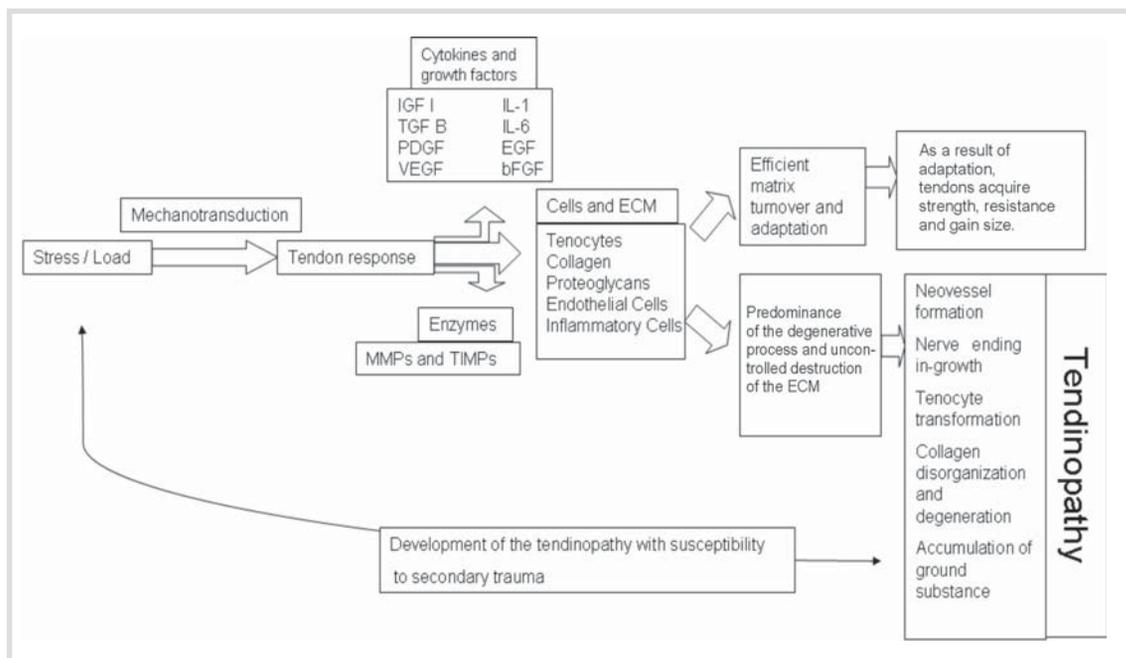


in tendons affected by tendinopathy [20]. Remodeling is a continuous process that is more efficient in tendons exposed to high stress. The response to a new load is called *mechanotransduction*, and it results in the rearrangement of the tissue structure [19]. Tenocytes are sensors between collagen fibers, which receive signals about the load and then transform extra-cellular matrix [15]. Tenocytes are responsible for production of matrix proteins and enzymes. The main enzymes involved in the matrix turnover are MMPs (metalloproteinases) [13]. Tenocytes synthesize MMPs in response to mechanical load, and the main role is played by MMPs type 1, 2, 8 and 9. TIMPs (tissue inhibitors of matrix metalloproteinases) are antagonists of MMPs. Secretion of the MMPs and TIMPs is a simultaneous process, which cooperates with matrix turnover [19].

As a result of tendinopathy tenocytes become larger and more round [44]. The general population of tenocytes increases. Variations in the amount of cytoplasm are specific – from limited cytoplasm, through small amount of visible cytoplasm, to lacuna formation of cytoplasm and chondroid transformation [45]. Cartilage metaplasia is the phenomenon found in advanced tendinopathy, however, calcifications and metaplasia into cartilage are rare

[27,45,46]. Healthy tendon regions contain tenocytes equipped with long processes for extra-cellular matrix infiltration. By contrast, tenocytes from tendinopathy regions, have a limited amount of short processes. The three-dimensional organization of tenocytes in healthy regions is characterized by cells located parallel to the long axis of collagen bundles and their even arrangement [47]. Authors claim that in pathological tendons tenocytes are randomly localized and the shape of nuclei is disrupted [47]. Tenocytes can affect angiogenesis and painful disorders. Recent studies have shown that tenocytes are capable of synthesizing adrenaline, noradrenaline, glutamate and substance P [48]. In the process of tendinopathy, apoptotic features may occur in tenocyte structures [13,46]. Increased numbers of apoptotic cells were observed in the supraspinatus tendon, patellar tendon and tibialis anterior tendon.

The loss of the collagen fiber arrangement is an important feature of tendinopathy [40,44, 47,49]. Collagen disorganization leads to tissue heterogeneity and loss of architecture. Collagen bundles are separated, disorientated fibers lose the axial arrangement [47]. Degenerated regions of tendons show differences in the distribution of fibril diameters with predominance of the small-diameter fibrils and decreased num-



**Fig. 2.** Schematic presentation of tendinopathy evolution. Stress or injury provoke tendon's healing response. Efficient adjustment provides improvement of the strength and resistance of the tendon. In face of inefficient recovery, the process develops into degenerative and leads to tendinopathy. Secondary trauma to the degenerated structure of the tendon will intensify the pathological process [13,20,24,27]

ber of large-diameter fibrils, compared to healthy regions [46,47]. Ruptured collagen fibers may be replaced with calcifications or lipid cells [10]. The characteristic „wavy configuration” of the fibers is irregular or completely lost. The collagen turnover rate is raised. There is increased amount of collagen, mainly of the third type, and elevated collagen III/I ratio [40,47]. Tendinopathy is characterized by raised proteoglycan amounts [3]. The examination of the Achilles tendon, which carries heavy loads, has shown increased density of Decorin, Biglycan, Lumican, Fibromodulin and Versican [50].

Tendinopathy is characterized by higher than in healthy tendons density of vessels and expansion of new capillaries [51,52].

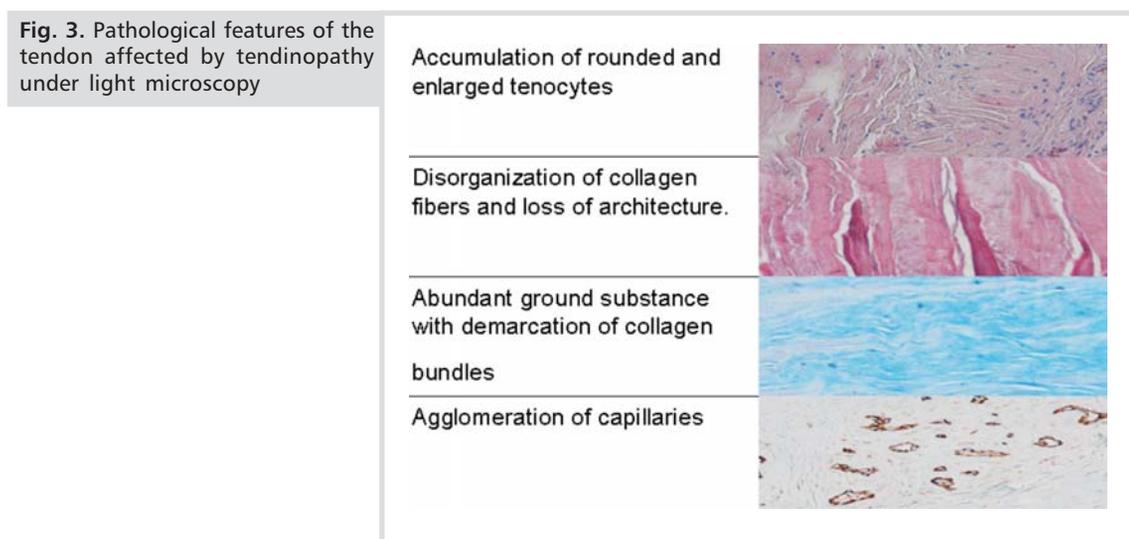
Usually inflammation is absent or limited [7,10,15,44]. Tendons in tendinopathy exhibit the same histopathological features and alterations [3,10,36,44,45,47]. The degenerative process involves all the components of the tendon (Fig. 3).

### NEOVASCULARIZATION AND ITS ROLE IN TENDINOPATHY

Nutrition of tendons depends on synovial fluid delivery and blood supply from the local vascular bed. Tendons are poorly vascularized compared with other tissues [43]. Vessels arise mainly from the musculotendinous junction, osteotendinous junction and connective tissue sheath, and are distributed longitudinally to the main axis of the tendon [42,43]. Certain tendons are more vulnerable to damage due to insufficient vascularity. Avascular regions with decreased vessel density are called *critical zones*

or *watershed areas* and occur in the Achilles tendon, rotator cuff tendons, biceps tendon and tibialis posterior tendon [10,30,31,32,42]. Neovascularization is absent in healthy tendons, but it is a common phenomenon in acute and chronic tendon pathologies. Animal tests have revealed formation of new blood vessels after acute tendon injury [43,53]. Numerous cases of chronic tendinopathy are characterized by intensive and rich angio-fibroblastic response [3,33]. Elevated levels of KI 67, b – FGF (basic fibroblast growth factor), PDGF (platelet-derived growth factor), EGF (endothelial growth factor), TGF β (tumor growth factor β) and VEGF (vascular endothelial growth factor) have been found in degenerated tendons [2,20,27,48, 49,54]. Vascular ingrowth and expansion often accompany painful conditions of tendons. It is believed, that nerve endings penetrate the tissue accompanying the blood vessel expansion, mostly by sensory and autonomic nerve fibers. Neurovascular ingrowth in painful areas of tendons has been described in a few studies, which clearly show a positive correlation [27, 48,55]. Nerve endings may also affect blood flow regulation.

Imaging techniques, such as ultrasonography, allow us to recognize and study tendinopathy. An important issue that distinguishes this technique is a possibility of a dynamic examination. Color Doppler and Power Doppler examinations have been commonly used to identify neovascularization processes [56,57]. Power Doppler uses focused strength of the Doppler signal and is able to obtain the signal from the smallest vessels [39]. Blood flows in healthy tissue are at low levels and usually cannot be



recorded. Power Doppler is a common and valuable technique for detection of pathological soft tissue blood flows, which are undetectable even for Color Doppler [56,57]. Revelations about the connection between pain, pathological vascularization and nerve ending ingrowth have opened new possibilities for ultrasound and targeted therapy [39]. Ultrasound is also useful in tendinopathy as a guide during injections to the tendons e.g. sclerosing injection therapy [48]. Nowadays, the role of ultrasonography in tendon pathology is developing, and it is becoming a helpful tool in diagnosis and therapy.

## SUMMARY

Tendinopathy is a common cause of complaints and patient referrals to orthopedic surgeons. At present, these conditions are increasingly reco-

gnized and treated, not only among athletes, but also in the general population. The terms *tendinitis* and *tendinosis* are being gradually abandoned and replaced with *tendinopathy*, which is the most correct term. The understanding of tendinopathy requires uniting known theories. Inflammation and degeneration coexist in tendinopathy, with degenerative processes being predominant. Are increased cellularity and vascularity a proof of tissue recovery and natural adaptive mechanism? Failures of the mechano-biological response and cell regulation are responsible for tendinopathy. Tenocytes, in reaction to the trigger factor, are led to imbalanced and chaotic production of extra-cellular matrix. The accumulation of new blood vessels in tendinopathy seems not to be a healing response. Studies on the neovascularization process convince, that it is a painful and irrecoverable phenomenon rather than an attempt of recovery.

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