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R E V I E W   A R T I C L E

# Tendon — function-related structure, simple healing process and mysterious ageing

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*Tendons are connective tissue structures of paramount importance to human ability of locomotion. The understanding of their physiology and pathology is gaining importance as advances in regenerative medicine are being made today. So far, very few studies were conducted to extend the knowledge about pathology, healing response and management of tendon lesions.*

*In this paper we summarise actual knowledge on structure, process of healing and ageing of the tendons. The structure of tendon is optimised for the best performance of the tissue. Despite the simplicity of the healing response, numerous studies showed that the problems with full recovery are common and much more significant than we thought; that is why we discussed the issue of immobilisation and mechanical stimulation during healing process. The phenomenon of tendons' ageing is poorly understood. Although it seems to be a natural and painless process, it is completely different from degeneration in tendinopathy. Recent studies of biological treatment reported faster and optimal healing of the tendons when augmented by growth factors and stem cells. Despite advances in biology of tendons, management of their injuries is still a challenge for physicians; therefore, further studies are required to improve treatment outcomes.* (Folia Morphol 2018; 77, 3: 416–427)

**Key words: tendon, tendon healing, ageing, collagen, therapeutic advances, training**

## INTRODUCTION

Although tendons seem to be relatively simple structures, studies from recent years demonstrated that they are characterised by a complex biology which is not completely understood. This knowledge is especially important for a more effective management of tendon injuries, improved training programmes for athletes and better prevention of problems related to tendon ageing. Difficulties in studying the biology of tendons are encountered because of limited access to undamaged human tissue samples. In this paper we present an analysis of results from contemporary studies on structure, process of healing and ageing of the tendons.

## STRUCTURE OF THE TENDON

Tendons are interposed between skeletal muscles and bones, designed to transmit force generated

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by muscles [4, 18]. They play an important role in locomotion, but also participate in joint stabilisation, shock absorption and, due to their innervation and presence of mechanoreceptors, provide sensory feedback for muscles [18]. Macroscopically a healthy tendon appears as fibro-elastic, solid structure in brilliant, white colour [62]. At microscopic and molecular levels they are characterised by a hierarchical structure, which guarantees high mechanical strength, endurance to repetitive loads and minimises the risk of failures and injuries [4]. As all connective tissue structures tendons are composed of fibres (mostly type I collagen), extracellular matrix (ECM; mostly proteoglycans, glycoproteins) and cells (predominantly tenocytes); despite their solid structure, tendons are highly hydrated and contain approximately 70% of water (mostly associated with proteoglycans).

Because of their mechanical role, most tendons are organised in a structure which can be compared to a synthetic climbing rope, consisting of a large number of thin twisted yarns (which transfer loads) contained within an outer sheath. However, in contrast to ropes, tendons contain additional functional units needed for vascular supply, and comprise cells which allow them to adapt to long-term changes in mechanical use — for instance related to sport activities. Moreover, division of each tendon into smaller components ensures a more uniform spread of loads and decreases the possibility of damage [32].

In tendons the primary load-carrying component is type I collagen — a protein characterised by a regular arrangement of amino acids, especially glycine, proline and hydroxyproline and extensive modification of the molecular structure during its synthesis [32]. A single collagen molecule (tropocollagen) consists of three polypeptide strands (alpha peptides), with a left-handed helical structure [18]. Alpha peptides are twisted together forming a right-handed triple helix stabilised by hydrogen bonds. The tropocollagen molecules both spontaneously and through guidance of fibroblasts arrange themselves into parallel aggregates, forming structures called fibrils, which are additionally stabilised by cross-linking bonds (aldol reaction) [18, 32, 54]. Fibrils aggregate into fibres, characterised by curly architecture, known as "wavy configuration" [30, 44]. Such crimped structure allows them to absorb energy, as was demonstrated by Franchi et al. [17] in the Achilles tendon of the rat [48]. In the physiological loading range such twisted structure can be temporarily deformed
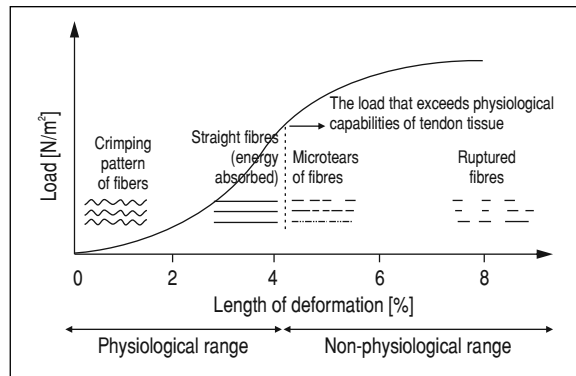


**Figure 1.** Load-deformation relationship chart. In the physiological range there is an energy absorption and elastic deformation of fibres. When the load exceeds the physiological capabilities, microtears of fibres are appearing and the curve enters the non-physiological range. Further, progressive load results in partial and complete rupture of fibres.

allowing dissipation of energy; however, stress which exceeds the physiological capabilities of the tissue will damage the fibres (Fig. 1) [44, 48].

Similarly as yarns in a rope, most collagen fibrils are arranged to the long axis of the tendon while a small group is located transversely to the main axis, providing resistance against transverse and rotational forces [18, 26]. Longitudinal collagen fibrils are packed into fibres — larger cable-like structures encapsulated by endotenon — a cuff of connective tissue providing vascular supply [44]. Bundles of fibres connected together forming larger structures called fascicles which are also encapsulated by individual endotenon cuffs [32]. The number and diameter of fascicles depends on the type of muscle and loads it is subjected to, but it may also vary from tendon to tendon and even within the same tendon [18]. Larger fascicles were found in the most loaded tendons — Achilles tendon and the smaller fascicles in tendons of the flexors and extensors of the digits [50]. In larger tendons, groups of fascicles are arranged into tertiary bundles, which are then enclosed by a two cuffs — the inner fibrous epitenon and the outer loose alveolar paratenon layer, both of which are carrying nerves, blood and lymphatic vessels [26]. Synovial tendon sheaths are common among tendons which are prone to high load, such as flexors in the human hand. Main role of the synovial sheath is production of synovial fluid, which provides lubrication to reduce the friction during movement and stress (Fig. 2).

Organised and balanced composition is responsible for superb biomechanical properties of tendons. Their strength results from collagen fibrils density,
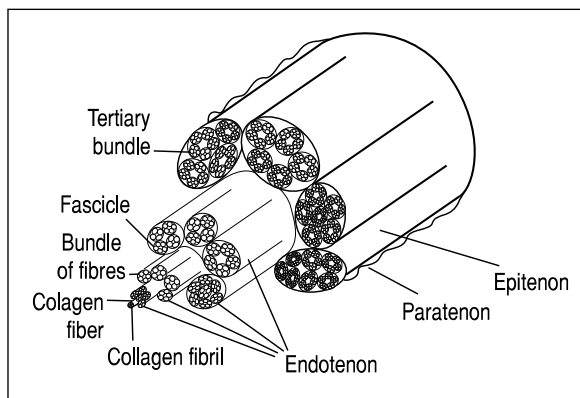
**Figure 2.** Structure of the tendon.

length, orientation and inter-molecular cross-links. Tendons are able to adapt to a new load via its cells and ECM. Physiological activity causes up-regulation of matrix turnover and increased synthesis of collagen molecules. Using a mural model it was shown, that collagen turnover was increased and enzymes responsible for collagen synthesis were up-regulated 48 h after physical exercises [42]. Similar behaviour was also found in humans, in a study involving microdialysis of peritendinous space of Achilles tendon among athletes, after 36 km of running [34]. It was demonstrated, that immediately after intensive exercise type I collagen synthesis and degradation were increased. However, 72 h after intensive exercise, type I collagen synthesis was still up-regulated, in contrast to decreased degradation of collagen molecules. Moreover daily training resulted in elevated synthesis of type I collagen after 4 and 11 weeks, while prolonged training (after 4 and 11 weeks) further decreased the ratio of collagen degradation. An illustrative example of exercise related remodelling of tendons was presented by Rosager et al. [51] who showed, that the cross sectional area of Achilles tendon in a human runners seems to increase with long-term mechanical loading. However, these authors were unable to identify a universal "pattern of training" allowing for an increase in tendon mass. Grzelak et al. [22] examined a group of professional, asymptomatic weightlifters, with mean training participation — 15.5 years. The study consisted of magnetic resonance examination and analysis of the mid-region of the patellar tendon. Authors noted the increased cross sectional area of the mid-region of patellar tendon — hypertrophy of tendon tissue. They concluded that this phenomenon was caused by the process of tendon's adaptation to

repeated high stress, particularly in the region where patellar tendon is the least susceptible for injuries. It seems that both exercise intensity and subsequent recovery time play an important role in tendon's intrinsic structure adaptation. Moreover, if training force exceeds tendon's adaptation capabilities, the degeneration occurs with developing tendinopathy. The state of the muscle attached to the tendon (i.e. its strength and elasticity) also contributes to tendon function and load absorption. Any muscular contraction causes increased load on tendon and can lead to tissue failure.

The ECM is a structure that creates a kind of scaffolding for cells, vessels and nerves and is composed of collagen molecules, proteoglycans, glycoproteins and other small molecules [62]. The main component of ECM is type I collagen, which constitutes approximately 95% of total collagen content in tendon tissue [62]. Among other collagen types found in tendons the most important is type III collagen, which is characterised by smaller and weaker fibres with reduced resistance and is typically found in endotenon and epitenon sheets [8]. Collagen type IV is found in membranes of vessels, types XII and XIV are localised within tendon insertion to the bones, while types V and VI are involved in creation of fibrils together with type I [50]. Another type of molecules found in ECM are proteoglycans — a group of different substances, represented by: aggrecan, biglycan, decorin, perlecan, agrin, laminin, versican, lumican, fibromodulin [32]. They are responsible for visco-elastic properties of the tendon and provide protection against compressive forces [62]. They also help retaining water molecules within the tendon, play a lubricating role and contribute to collagen fibrils fusion [32, 50]. The content of proteoglycans is increased in tendons subjected to high loads, as seen in the Achilles tendon — which contains relatively high amounts of decorin, biglycan, lumican, fibromodulin and versican [60, 61]. The last group of molecules found in the ECM are glycoproteins, which play an important role in cell-to-cell interactions, adhesion and include tenascin C, fibronectin, and thrombospondin. Together with integrins, a class of proteins which link the ECM with the cytoskeleton, they form a complex system which transduces mechanical stimuli to the cells cytoplasm in a process called mechano-transduction [32]. This process allows tendons to gather information regarding loads they are subjected to and transfer it into tenocytes. This way mechanical loads can modify the

intracellular metabolism of tenocytes and affect the release of growth factors, cytokines and components of the ECM [32].

The dense network of collagen fibres and ECM of tendons contains a large number of cells. The main population of tendon cells are local fibroblasts — tenocytes [18]. Tenocytes are equipped with a numerous of extensions to penetrate the extra-cellular matrix and represent various phenotypes — from rounded to elongated cells [32, 49]. Rounded tenocytes — similar to chondrocytes, are located predominantly within entheses (insertional zone), while cells with elongated shape are located in weight-bearing areas [49]. The main role of tenocytes is the synthesis of the collagen molecules and maintenance of proper composition of the ECM. There is a constant interaction between ECM and tenocytes, which results in remodelling and subsequent changes, e.g. adaptation, tendinopathy, rupture of the tendon tissue [46]. A much smaller population of cells residing in tendons are endothelial cells, which tend to line the interior of the capillary vessels and play an important role in coagulation, thrombolysis, vascular tone, angiogenesis, inflammation and tissue repair [46]. Another group are the mast cells, which are associated with nerve endings and axons. Their role is still unclear, but some authors suggest involvement in pain mediation and ECM homeostasis regulation [32]. Chondrocytes are occasionally seen at tendon-bone junctions-entheses. The enthesis region is a region characterised by rounded tenocytes which create Indian-file [49]. The transition from tendon tissue, through fibrocartilage, calcified fibrocartilage to mineralised bone is typical. The abundant type I collagen molecules are supplemented with type II, IX and XI collagen and increased amount of proteoglycans is characteristic. As mentioned previously tendons play not only a mechanical role but also act as force sensors involved in proprioception and regulation of muscle contraction force. The innervation of tendons originates from surroundings muscles and cutaneous nerves; nerves are distributed in the epitenon and paratenon. Although some nerves terminate with free endings, a large number of axons is connected to three types of receptors: Ruffini corpuscles — called type I, Pacini corpuscles — called type II (mainly at the insertions to the bones) and Golgi tendon organs called type III — mainly at the insertion of tendons into muscles [1, 5]. Free nerve endings serve as pain receptors and their highest
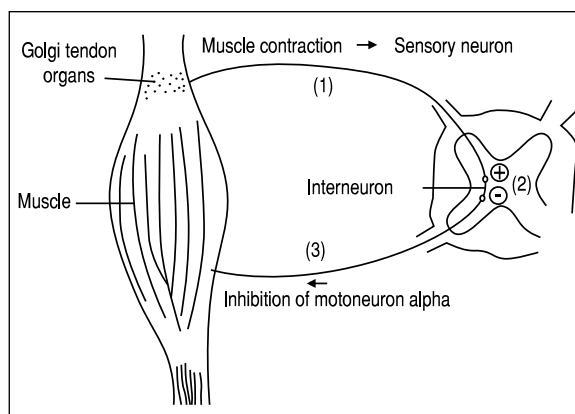


**Figure 3.** Golgi tendon reflex is a protective feedback mechanism controlling the muscle tension. When the muscle contracts, muscle tension is increasing and Golgi organs send impulses by the afferent neuron (sensory neuron 1b) to the central nervous system — spinal cord; (1) — In the spinal cord, the sensory neuron activates the interneuron; (2) — Interneuron inhibits the motoneuron alpha and inhibited motoneuron alfa cause a relaxation of agonist muscle; (3) — Antagonistic muscles are additionally activated by efferent fibres and contracted.

density was found in the smallest tendons responsible for precise movements as well as in the proximity of the capillary vessels in tendons [1]. The Golgi, Ruffini and Pacini nerve endings are mechanoreceptors activated by stretching or compression. Golgi tendon reflex protects the muscle and tendons from excessive force and damage and is associated with eponymous tendon organs which react to the excessive contraction of musculotendinous unit. They fire electrical signals, which travel through sensory neurons and after switching by an interneuron downregulate motor neurons affecting muscle contracture (Fig. 3) [23].

## HEALING OF THE TENDON

Healing of tendons has been extensively studied using animal models, usually a model of acute rupture of a healthy tendon [1]. In contrast, data regarding human tendons is limited and comes mostly from studies of degenerated tissue with advanced tendinopathy. In sports acute tendon injuries are usually accompanied by extrinsic factors — training errors, inadequate equipment, participation in competitive events and spontaneous tendon ruptures may often appear without previous clinical symptoms [28, 50]. Kannus and Józsa [29] studied 891 samples obtained from patients who underwent acute spontaneous Achilles tendon rupture. They noted enormous prevail of degenerative process among samples of Achilles tendon, which preceded the rupture [1, 29]. It
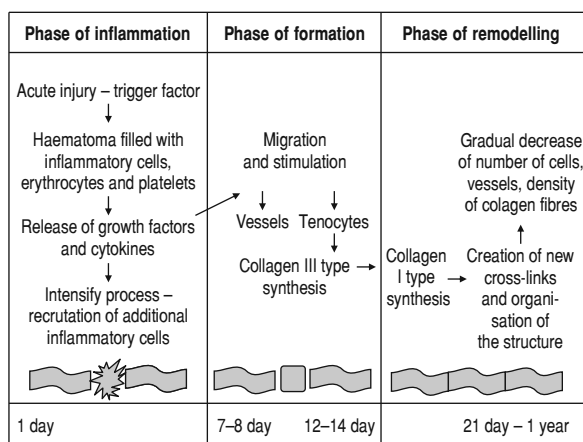
| Phase of inflammation | Phase of formation | Phase of remodelling |
|---|---|---|
| Acute injury – trigger factor ↓ Haematoma filled with inflammatory cells, erythrocytes and platelets ↓ Release of growth factors and cytokines ↓ Intensify process – recrutation of additional inflammatory cells | Migration and stimulation ↓ ↓ Vessels  Tenocytes ↓ Collagen III type → synthesis | Gradual decrease of number of cells, vessels, density of colagen fibres ↑ Collagen  Creation of new I type → cross-links synthesis  and organi- sation of the structure |
| 1 day | 7–8 day    12–14 day | 21 day – 1 year |

**Figure 4.** Diagram describing stages of healing process and its development.

is therefore generally accepted that acute ruptures of tendons are usually preceded by some degree of degeneration of tissue structure; the alterations are important factor predisposing to injury [28, 50]. Chronic tendon pathology may result from various intrinsic factors (chronic diseases: endocrine, rheumatoid; gene defects, malalignment of the limbs, microtrauma and overuse of the tendon), supplemented by extrinsic risk factors (overuse, high-impact sports) [28].

The repair of tendon lesions consists of three main phases, essential for soft tissue healing: inflammation, formative phase — divided into proliferation and differentiation periods, and remodelling phase (Fig. 4) [5].

In the beginning, the trigger factor — injury, promotes inflammatory process, which lasts about 7–8 days [5]. Acute phase starts with formation of haematoma adjacent to the tendon lesion [15]. Inflammatory cells present in the haematoma — neutrophils, macrophages and platelets, begin releasing cytokines and growth factors in the injury area. These substances initiate the next phase, stimulating cell proliferation and migration of tenocytes, angiogenesis and chemoattraction of additional inflammatory cells. These inflammatory cells release mediators which upregulate proliferation of tenocytes from undamaged tendon fragments and recruit fibroblasts from adjacent structures — the endotenon, epitenon, paratenon [19, 58]. The proliferative phase typically lasts up till 21th day after the injury. By this time tenocytes become the dominant population of cells in the lesion area. Initially, during the proliferative

phase, fibroblasts synthesize type III collagen, which is arranged randomly, elastic and prone to injury. Subsequently, since days 12–14 tenocytes begin producing type I collagen, which is being arranged in fibrils in a process called "fibrilogenesis", which increases the strength of the tissue [5]. Afterwards fibrils consolidate together end-to-end ("linear growth") and side-to-side ("lateral growth"), gradually improving mechanical properties of the damaged region [5]. The last phase — remodelling, begins 3–6 weeks after injury and ends even 1 year later [5]. During this phase the number of cells, vascularity and collagen fibres density is slowly decreasing, while tendon's elasticity and strength are improving [54].

The recovery rate of damaged tendons is slower when compared to bone and skeletal muscles. It is a result of a relatively slow metabolism of tenocytes (the oxygen consumption is 7.5 times lower than that of skeletal muscles), which physiologically allows them to endure stress during long term loading [5, 38, 54]. Low metabolic rate and predominance of anaerobic process in tenocytes decreases risk of failure related to ischaemia; however, it results in slower recovery of tendon tissue [55]. Recovery times may vary between individuals and can be prolonged by loading exceeding physiological values, slow synthesis of structural proteins or poor perfusion (as in diabetes or smokers). Moreover, if the stress or load applied during recovery exceeds the threshold of possible adaptation or reparability, there is a change in profile of mediators released in the damaged area, which leads to degeneration [5]. In such case there is a chaotic production of extra-cellular matrix by tenocytes and chaotic expansion of new capillary vessels (so-called neovascularisation); consequently, this results in decreased mechanical durability of the tendon (Fig. 5).

Degeneration results in formation of tissue prone to succeeding injury and creates the vicious circle; it manifests as tendinopathy. Although different, often confusing, terms are used to describe tendons' disorders, tendinopathy seems to be the most widely accepted and suitable term. Tendon cells affected by tendinopathy differ from healthy tenocytes and their metabolism is modified due to altered expression of almost 983 genes [4]. The aetiology of tendinopathy seems to be multi-factorial, involving intrinsic and extrinsic factors [31]. As tendinopathy is related to tendons' pathology, enthesopathy refers to pathology of tendon-bone junctions. Enthesis is the region "where tendon meets bone" [7]. The structure of
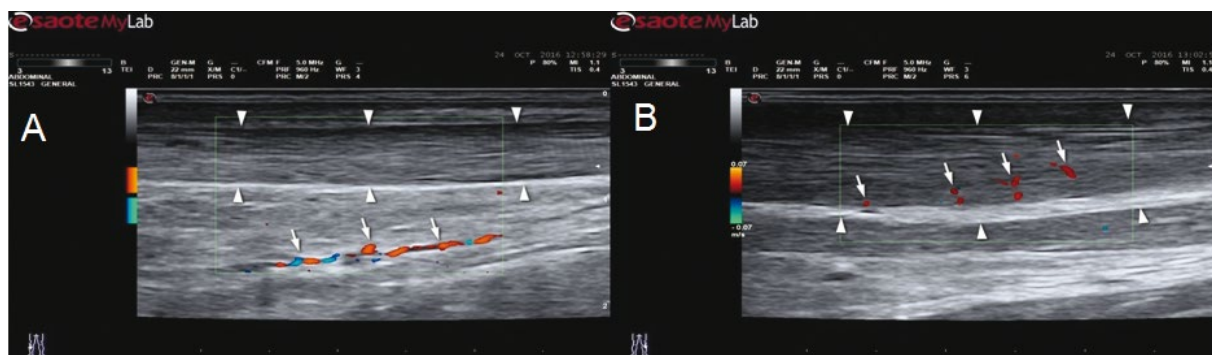
**Figure 5. A.** Ultrasound appearance of healthy Achilles tendon. White arrowheads indicate margins of healthy Achilles tendon and white arrows indicate regular vessel. **B.** Ultrasound appearance of tendinopathy of the Achilles tendon. White arrowheads indicate local thickening of the Achilles tendon structure and white arrows indicate pathological capillary vessels, formed in the process of neovascularisation.

enthesis corresponds to its function, exposure to high load and consequently is prone to injuries. The Achilles tendon insertion to the calcaneus consists of fibres originating from the three essential subunits: the soleus muscle, the medial and lateral heads of the gastrocnemius muscle. These components or so called "subtendons", heading to the enthesis of the Achilles tendon, are twisting and bending at a different angle in distinct subunits. It may have obvious further mechanical and clinical implications [45]. Osteotendinous junctions are common areas of overuse trauma, especially activity-related. Enthesopathies of the lateral epicondyle of the humerus, the lower pole of the patella, the Achilles tendon insertion and the plantar fascia of the heel prevail among athletes. Interestingly in this condition, there seems to be a superior role of the degeneration over the inflammation [7].

Immobilisation of tendon tissue is also associated with pathologic changes within the tissue, presumably due to lack of mechanical stimuli. It results in decreased strength, visco-elastic properties and finally tissue atrophy. Collagen fibres are becoming thinner, disorganised, angulated and the net of capillary vessels is significantly reduced. These all transformations result in decreased resistance to stress and load [28]. For these reasons the tendon repair process should be supported by mechanical stimulation of tissue [5]. When inflammatory phase is over, mechanical stimulation — stretching of the healing tendon is thought to have an important influence on tissue mechanobiological properties and structure arrangement [28]. Collagen, which is not under stress during the proliferative and remodelling phases, is weaker and its hierarchical structure is disturbed [28]. This was demonstrated in a study on rats, which showed that

mechanical stimulation ("activity cage") had positively influence healing process, improving the strength of the tissue [59].

Immobilisation of tendon may cause also an adhesion phenomenon. Tendons of flexors and extensors of the hand are a particular risk group. Granulation tissue which is formed during healing response may form adhesion between the tendon and its sheath; consequently, most modern rehabilitation protocols of these tendons involve early mobilisation [28, 52]. The most common tendon exposed to rupture, Achilles tendon, heals spontaneously immobilised for a few weeks [5]. When the leg is in a cast, the stress applied on Achilles tendon depends on the plantar flexion in ankle joint, with lowest values seen in maximum plantar flexion [3]. The effect of plantar flexion on healing process are not fully understood, since there are few studies which examined electromyographic activity of triceps surae during the period of immobilisation. Moreover, some of them demonstrated contractile activity of plantar flexors present at various ranges [5]. Understanding this complex muscular balance is important when using heel lifts and regulated cam-walkers to regulate the strain applied to immobilised Achilles tendon [3]. Although recent studies revealed that earlier mobilisation upgrade the healing process, further research is required to determine the timing and special rehabilitation protocols which safely ensure optimal tendon healing [5].

As mentioned previously, healing of tendon lesions is regulated by a complex network of cytokines and mediators which dynamically interact during healing process [40]. The presence of different types of growth factors is necessary in specific time to achieve recovery, it was therefore assumed, that by applying them in optimal doses, it would be possible to support

**Table 1.** Main growth factors involved in the process of tendons healing and their activity in different stages of recovery

|  | Phase of inflammation | Phase of formation | Phase of remodelling |
|---|---|---|---|
| Transforming growth factor-$\beta$ | + | + |  |
| Insulin-like growth factor-1 and -2 | + | + |  |
| Vascular endothelial growth factor |  | + | + |
| Platelet-derived growth factor | + | + | + |
| Basic fibroblast growth factor |  | + | + |

the recovery of tendon tissue [14, 40]. It is currently believed that five growth factors play the most important role in the healing process of tendons: insulin-like growth factor-1 (IGF-1), transforming growth factor-$\beta$ (TGF-$\beta$), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) (Table 1) [40].

Their activity is essential for each phase of healing process but strictly depends on dose, specific receptors, interactions with other molecules [40]. PDGF and TGF-$\beta$ are released from platelets immediately after the injury of tendon tissue [14]. The inflammatory phase is initiated and additionally IGF-1 and IGF-2 are released [40]. Interleukin-1, interleukin-6 and tumours necrosis factor are pro-inflammatory cytokines and after human anterior cruciate ligament rupture their level is elevated and is gradually decreasing in subsequent phases of tendon healing process [14]. IGF-1 is an important growth factor during inflammatory and formation phase. IGF-1 stimulates collagen production, intense migration and proliferation of fibroblasts [40]; animal studies revealed its increased secretion in rabbit medial collateral ligament (MCL) for 3 weeks after acute injury. IGF-2 similarly increases synthesis of collagen molecules [41]. TGF-$\beta$ is highly active during inflammatory phase; its actions include: stimulation of collagen production (particularly type I), regulations of proteinases, regulation of cells migration and proliferation. Studies on rats' patellar tendon showed elevated levels of TGF-$\beta$ for 8 weeks after injury [40]. Study of rabbit MCL healing revealed increased secretion of TGF-$\beta$ for 3 weeks after injury [41]. PDGF is released immediately after tendon injury, stimulates the production of other growth factors and is present in formation and remodelling phases [40]. VEGF levels are elevated after the inflammatory phase, during formation and remodelling phases. Its main role is stimulation of angiogenesis process [40]. The bFGF also stimulates angiogenesis process, regulates cells migration and proliferation, this cytokine is present during formation and remodelling phases [40].

In recent years, there has been a growing interest in the application of platelet rich plasma (PRP) in injuries of soft tissue structures. This is related to the fact, that platelets contain relatively high amounts of growth factors present in healing process: PDGF, IGF-1, VEGF, bFGF, TGF-$\beta$, EGF and preparation of PRP is a simple and inexpensive procedure [16]. The intention is to augment the natural healing process through the action of certain growth factors. Studies on animal models showed that PRP injections into patellar tendon, Achilles tendon and tendons of digits flexors after injury gave positive results and improved the healing response [16]. Human studies of PRP injections are limited. Two studies of PRP injection for tennis elbow demonstrated relief of pain, reduced thickness of tendons, decreased neovascularisation and hypoechoic changes in the structure of tendon tissue confirmed by Doppler ultrasound examination [12, 56]. On the other hand, a different group of authors examined 54 patients with chronic Achilles tendinopathy, treated with PRP injections and training. They did not report better outcomes among patients treated with PRP injections; there was no improvement in assessment of pain and activity [13].

As mentioned previously, tendon healing involves recruiting cells which form tenocytes and contribute to ECM production. Studies from recent years suggested that mesenchymal stem cells (MSCs) could be used in management of tendon lesions. This is because of their high potential for proliferation and differentiation into various cell lineages. Moreover, MSCs are prevalent in bone marrow which can easily be harvested from the iliac crest. Later, stem cells can be isolated using relatively simple protocols. Alternatively, MSCs are obtained from adipose tissue [9]. It must be however underlined that the ideal source of stem cells, optimal concentration and delivery method for clinical use are yet to be determined [9]. Animal models showed positive results of MSCs application in tendon repair process. Authors obtained MSCs from femurs and tibias of rats and injected to the ruptured Achilles

**Table 2.** The most frequent areas of tendon disorders among participants of different sport-activities

| | Achilles tendon | Forearm extensor and flexor tendons | Tibialis posterior tendon | RCT and LHBT | Triceps tendon | Patellar tendon | Iliotibial band | Hamstring tendons |
|---|---|---|---|---|---|---|---|---|
| Running | + | | + | | | + | + | + |
| Tennis | | + | | + | | + | | |
| Golf | | + | | | | | | |
| Javelin throwers | | + | | + | + | | | |
| Baseball | | + | | + | | | | |
| Basketball | + | | | | | + | | + |
| Volleyball | + | | | | | + | | + |
| Badminton | + | | | | | | | |
| American football | | | | + | | | | |
| Swimming | | | | + | | | | |
| Football | + | | | | | + | | + |
| Squash | | | | | | + | | |
| Cycling | | | | | | | + | |

LHBT — long head of biceps tendon; RCTs — rotator cuff tendons

tendon [53]. After 12 weeks the strength of tendons was significantly improved. Immunohistochemical evaluation showed increased localisation of MSCs in the area of the repair zone [53]. Bone marrow-derived MSCs have been shown to improve the mechanical properties of rabbits' patellar tendons [6]. Grafts of semitendinosus tendon enriched with MSCs were used in the anterior cruciate ligament reconstruction in animal study on 48 adult rabbits. After 8 weeks the mechanical properties of grafts were improved [36]. The application of MSCs has been studied with the equine superficialis flexor digitorum tendons, which is analogous to the human Achilles tendon. MSCs treatment of superficialis flexor digitorum tendons overstrain injuries of the racehorses was associated with a reduced tendon re-injury rate and improved collagen fibre organisation as measured by ultrasound. The follow-up was minimum 2 years and there were no adverse effects [20].

There are a modest number of human orthopaedic studies that evaluate the MSCs [9]. A few studies examined the effect of MSC on healing process of tendons. Ultrasound controlled study of lateral epicondylitis on 12 patients showed positive outcomes in clinical and ultrasonographic scale [11]. Another study of 60 patients with patellar tendinopathy noted clinical improvement in a group treated with MSCs injections [10]. The study was supported by ultrasound examination and revealed reduction in tendon thickness after stem cells therapy.

## TENDONS IN THE ATHLETES

A tendon with 1 cm$^2$ cross section area is able to bear the weight of 500–1000 kg, which is extraordinary and astonishing result; however, regular training can further improve tendons strength, elasticity and cross-sectional area [1, 55]. In comparison to inactive individuals intensively trained athletes have thicker cross-sectional area of the Achilles tendons which are more resistant to failure [28]. Still, disorders of tendons represent about 30% of orthopaedic consultation and tend to be particularly widespread among athletes (Table 2) [4].

Common clinical symptoms include pain in the area of tendon, intensified by training, feeling of stiffness after training or in rest, swelling, tenderness [1]. Tendon pathology affects almost 30% of running athletes [55]. Forearm extensor and flexor tendons disorders are widespread among tennis players (up to 39.7% of tennis players), golf players, throwing athletes — especially javelin throwers and baseball players [1, 21]. Lateral epicondylitis (tennis elbow) and medial epicondylitis (golfer's elbow) are typical for activities demanding overhead or repetitive arm actions [31]. Achilles tendon is the biggest, the strongest and the most often injured tendon of human body. This magnificent connective tissue structure is bearing the forces of 12.5 times of body weight during running [55]. Achilles tendinopathy occurs in 5.9% of seniors and 50% of elite athletes [31]. Degenerative altera-

tions in Achilles tendon structure are commonly found among asymptomatic patients during ultrasound examination and may lead to spontaneous tendon rupture. Achilles tendon is especially prone to injury among patients who take steroids and fluoroquinolone antibiotics [48]. Extrinsic risk factors (sport activities, training errors, fatigue, equipment) and intrinsic risk factors (endocrine diseases, oral contraceptives, obesity, hormone replacement therapy, increased foot pronation) are not without significance [1]. Majority of Achilles tendon ruptures is related to sport activities, with dominance — 53% of running and jumping sports (volleyball, basketball, badminton) [21]. The prevalence of Achilles tendinopathy among runners is 11% and soccer players is 11% [48]. Inactive patients exposed to risk factors are also concern as prone to Achilles tendon disorders. In 41% of patients with symptomatic Achilles tendon tendinopathy symptoms occur in contralateral extremity during 8-year period [31]. Tibialis posterior tendon disorders are common among runners; degenerative changes are also common in the elderly and often associated with valgus, flat-foot deformation, overpronation of the foot, impoverished vascularisation in the area behind medial malleolus, ligamentous laxity [1]. Rotator cuff tendinopathy is a common pathology in the mid-aged and elderly patients; however, it also often occurs in swimmers, throwing sports such as javelin throwers, baseball, tennis, volleyball, and American football players [1, 31]. Triceps tendon disorders are common among throwing athletes [1]. Patellar tendon tendinopathies represent two thirds of all pathologies of the knee induced by volleyball or basketball — repetitive jumping sports [22, 31]. Other sports that expose to this kind of disorders are football, tennis, squash and running [9, 48]. Iliotibial band pathology is present in 14% of repetitive trauma of the knee joint and occurs in cyclers, runners, joggers and skiers. Hamstrings disorders represents 3% of knee joint injuries, particularly among sprinters, jumpers, footballers; moreover hamstring tendons commonly serve as an autograft for a reconstructive surgery in the orthopedic field [24, 31].

Conventional methods of tendinopathy treatment are aimed at reduction of pain and inflammation [31]. These methods do not have an influence on pathological tissue structure recovery. Eccentric training is currently thought to be the most efficient treatment in chronic tendon disorders. The main principles of this method of treatment are slow speed, low in-

**Table 3.** Diagram describing structural changes in ageing tendon

| Ageing of tendons and alterations of their structure and tissue activity |
|---|
| Reduced blood flow and decreased number of capillaries |
| Increased lipid storage |
| Slower turnover rate of the collagen |
| Variations in crimping pattern of fibres |
| Decreased content of water, proteoglycans and glycoproteins |
| Thicker collagen fibres with disorganisation of the hierarchical structure |
| Reduced number of tenocytes with alterations in their structure |
| Accumulation of the advanced glycations end products |
| Increased number of non-reducible cross-links between collagen molecules |

tensity, gradual intensification [31]. Eccentric training stimulates remodelling of the tendon structure, improves the tendons mechanobiological properties and can prevent relapse of disorders.

## AGEING OF THE TENDONS

The phenomenon of ageing is unavoidable and should be considered not as pathology but a natural process. It must be underlined, that ageing is not only a wear and tear phenomenon, but is also associated with changes of gene expression and apoptosis which lead to decreased healing potential and performance of musculoskeletal system [57]. Although the mechanism driving tendon ageing are poorly understood, they result in well characterised structural changes within the ECM, predominantly related to changes of post-translational modifications in collagen (Table 3) [43].

These changes include accumulation of glycation end products and additional cross-links; a tendency for production of enlarged collagen fibrils was also documented [47, 50]. The end result of these processes is stiffness and resistance to degradation enzymes involved in tendon collagen remodelling, resulting in slower turnover of the ECM [57]. In ageing tendons the number of tenocytes is usually reduced, with alterations to their structure — they become longer, slender and their nuclei are filling almost all interior of the cell with complete reduction of other structures and organelles [18, 25]. Ageing of tendons is associated with structural changes in the ECM. This includes thickening of collagen fibres ad disintegration of their hierarchical structure [18]. In most cases the wavy arrangement of fibres seen in

healthy tendons is disturbed, possibly as a result of cumulative effect of microinjuries occurring throughout patients' life [57]. This is accompanied by poorer tissue hydration, decreased content of proteoglycans and glycoproteins and increased lipid storage within the tendon [2, 57]. Reduced perfusion due to a diminished number of capillaries is also observed and neovascularisation process is usually absent [18]. The resulting hypoxia and impaired nutrition further contributes to degenerative changes and deterioration of mechanical properties of the tendon. Although this process is asymptomatic in most individuals, it results in increased susceptibility to injuries in the elderly. Phenomenon of ageing depends on numerous factors, such as genetic predispositions, lifestyle, and concomitant diseases, and its progress is highly individual. Interestingly, the extent of this process varies between different muscles and although some tendons may be unaffected, the overall failure rate is elevated, so that up to 30% of population older than 70 year has symptomatic tendon degeneration. This especially applies to rotator cuff tendons (RCTs), which degeneration rate increases with age. Authors noted that RCTs degeneration and tears are a natural and gradual process. This phenomenon starts after the age of 50 and increases with time, involving 50% of dominant shoulders in patients in their 70s and 80% of shoulders in patients in their 80s [39, 57]. The supraspinatus tendon is the most vulnerable and prone to the degeneration. Multiple theories were formulated to explain this phenomenon: theory of Codman's critical zones, which describes avascular region within the insertion of the supraspinatus tendon to the humeral head and the Neer's theory, which points at subacromial impingement as a main reason of RCTs degeneration [48]. The long head of biceps tendon (LHBT) tendinopathy is also developing with age. The LHBT degeneration is strictly and proportionally associated with occurrence of RCTs tendinopathy — 41% [31]. It is thought, that impingement and damaged layer of RCTs predispose LHBT to chronic pathology. Lateral epicondylitis is 2–3.5 times more frequent among persons in fourth and fifth decade of life. Tennis players who train more than 2 h per day are at particular risk [31]. Achilles tendon is also getting more prone to trauma with age, which is certainly based on the degeneration process. Typical spontaneous rupture occurs between 30 and 55 years of age in athletes as well as inactive persons [1]. Numerous additional risk factors expose tendons to pathology in the old age. Hypothyroidism leads to accumulation of glycosaminoglycans and weakening of the tendon structure. Several commonly used drugs may also affect mechanical properties of tendons. Corticosteroids — oral application or injection, decrease the general collagen production. This is particularly important since this class of drugs is used in local injections to relieve symptoms of tendinopathy or tenosynovitis. Vitamin C deficits lead to scurvy and defects of collagen molecules [57]. Women who suffer from hypertension, diabetes mellitus and arthropathies are particularly exposed to injuries of tibialis posterior tendon [48]. Fluoroquinolones may also induce pathological alterations in tendon structure. Symptoms may occur hours after initiation of therapy and even after few months after the end of treatment. Recovery is significantly slower than after common injury [35]. Similarly doxycycline antibiotics inhibit collagen proteases and reduce mechanical properties of tissue, while on the other hand insulin, oestrogen and testosterone — increase collagen production [49, 57].

Although most research regarding tendons focused on athletes, it was also demonstrated that moderate exercises and sport activity influence positively ageing tendons' structure and adaptation [57]. Exercises conducted in a long-term lead to improvement in collagen synthesis, metabolic enzymes concentration, ultimate tensile and strength, cross-sectional area, volume of proteoglycans and load to failure of the tissue [37]. During recreational sport activities a few guidelines must be followed: warming-up before sport activity (increasing the elasticity of musculotendinous unit and smoothing muscular contractions), no rapid changes in activity, carefully selected equipment (especially footwear), safe weather conditions, and frequent stretching of tendons [27].

## SUMMARY

The structure of tendon is strictly related to their function. Organised, hierarchical and balanced composition allows for optimised biomechanical properties and protects from injuries. Recovery of the tendon tissue after injury is essentially the same as in other soft tissues, but relatively slower. Despite the apparent simplicity of healing this process is poorly understood and may lead to deterioration of mechanical performance of the tendon. Moreover

when local load exceeds the threshold of possible adaptation and reparability, healing shifts into degenerative process. Ageing of the tendons seems to be an unavoidable asymptomatic natural process, which is however associated with an increased risk of injuries.

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