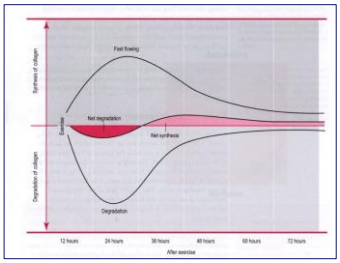
Tendinpathie O.E.

6

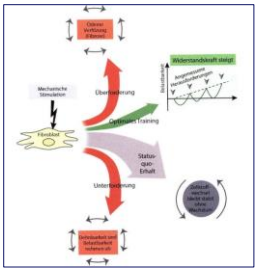
Opleiding fasciatherapie F.I.T.
Module onderste extremiteit

Short description of content: Although tendinopathies are very common there is still much not known about the pathology and the most effective treatment. This presentation describes what is known through research and offers a novel way of looking at tendinopathies from the view of what the role of the groundsubstances might play in tendon eleasticity.
Learning objectives: Be familiar with the state of the art approach to tendinopathies of the lower extremities. Beside know adjunct therapy possibilities based on the hyaluron theory

Oorzaken tendinopathieën



- Overuse (na underuse?)
- Genetische predispositie
- Veroudering
- Overgang
- Metabole aandoeningen
- Sensitisatie



Afbraak is sterker dan de reparatie

Er is nog veel onderzoek nodig!

2

<<Tendinopathies represent a substantial part of the occupational disorders of the passive locomotor apparatus and increase in prevalence as intense sport activities become more common, in particular in the older segments of the population (Maffulli et al., 2003). Tendinopathies account for up to 30 per cent of rheumatological consultations in primary care in the UK (Millar et al., 2013). Tendinopathies are often associated with conditions of overuse and are frequent in running, athletics (annual incidence up to 9 per cent; Lysholm and Wiklander, 1987) and sports involving overhead manoeuvres (Kettunen etal., 2011). Midportion and insertional tendinopathies are distinguished as separate clinical conditions. Most frequent, and discussed below, are tendinopathies of the Achilles tendon, the patellar tendon, the tendons of the rotator cuff and of the extensor carpi radialis brevis (tennis elbow). Tendinopathies can take the form of tendinosis or tendinitis sometimes associated with peritendinitis. Tendinosis presents as disorganization of the collagen matrix of the tendon associated with an increase in ground substance (glycosaminoglycans and proteoglycans) separating collagen fibrils. In later stages, rounding of tenocytes and hypercellularity is seen, and vessels, as well as nerves, invade the tendon, which, under normal conditions, is poorly supplied with blood vessels and nerves. Early tendinosis, as such, is not associated with pain. Inflammafion and associated pain mostly occur in the tissues and membranes around

tendons (peritendinitis) or at the tendon insertions that are better supplied with vessels and in chronic and later stage tendinosis (see Ackermann and Renstrom, 2012). The aetiology of tendinopathies is currently subject to intense investigation, whereby a number of mechanisms have been identified. However, their relevance and role in healthy healing of tendons versus development of tendinopathy remain debated.

Tendon tissue belongs to the category of mechanically sensitive tissues that respond to mechanical stress by upregulating gene expression of collagen proteins. Proteins synthesis is reported to be co-regulated in muscle and tendon tissue, and peaks at 24 hours after stress, but remains elevated beyond 72 hours (Miller et al, 2005). This indicates a transcriptionally regulated stimulation of collagen synthesis similar to the transcriptionally regulated adaptations of skeletal muscle tissue with repetitive loads. On the other hand, collagen catabolism as a consequence of loading also occurs. The peak of collagen catabolism after repetitive loading is assumed to occur earlier than the peak of collagen synthesis (Maffulli et al, 2010). It has thus been hypothesized that to frequent (over)loading of tendons could lead to a negative collagen balance and to a long-term catabolic situation in tendon tissue (see Ackermann and Renstrom, 2012). There is evidence for inflammation, presence of macrophages, T cells and mast cells in early overload tendinopathy (Millar et al, 2010). It has further been suggested that tendon tissue hypoxia might play a key role in early tendinopathies driving the synthesis of proinflammatory cytokines and apoptosis (Millar et al, 2012). Vessel in-growth has also been attributed to hypoxia and concomitant upregulation of HIF-la, known to be a potent stimulator of VEGF (vascular endothelial growth factor). It is suggested that in-growth of nerves occurs together with, or subsequent to, vessel in-growth from the para- and epitenon (Messner et al, 1999). Changes to the status of the nociception in tendons are also discussed as important factors in later stage painful tendinopathy (Dean et al, 2013). In this context, presence of the neuropeptide substance P and increased pain-related glutaminergic signalling play major roles.

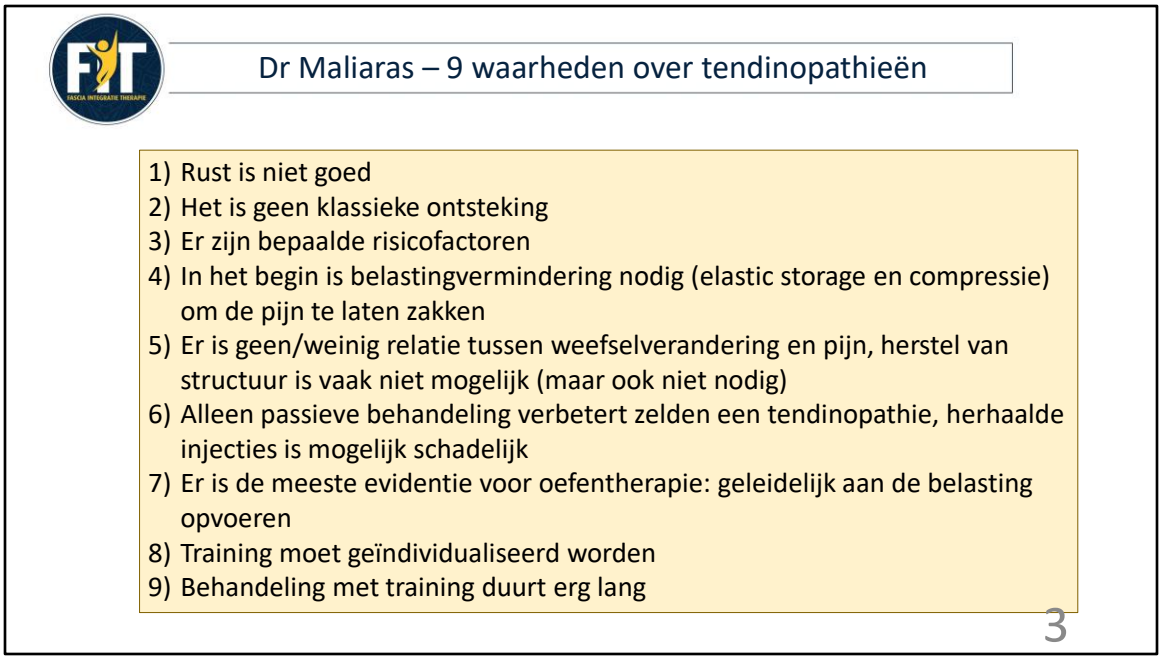
Eccentric exercise is recognized to be the conservative treatment of choice for tendinopathies, with some reviews indicating that addition of shockwave treatment to eccentric exercise may even be more effective (Ackermann and Renstrom, 2012; Rowe et al, 2012). Despite the fact that eccentric exercise is generally accepted as a first-line therapeutic measure, there is no consensus as to the mechanism responsible for the observed therapeutic benefits. A systematic review of the literature finds no support for observable structural changes (collagen or matrix) as a consequence of eccentric exercise training (Drew et al, 2012). Instead, these authors suggest that neuronal, biochemical or myogenic changes might be responsible for the therapeutic benefits. The specifics of the use of eccentric exercise in Achilles, patellar, rotator cuff and lateral epicondyle tendinopathies are discussed below. Unfortunately, due to the lack of large-scale prospective studies with adequate

controls, the evidence for effectiveness of eccentric exercise (and adjunct therapies) remains sketchy. Hopeler 2015>>

<<The exact pathogenesis behind development of tendon overuse – tendinopathy – is still not completely solved. Magnusson 2018>>

<<Tendons can withstand considerable force, but repetitive movements, both in relation to sports and occupational loading, often lead to overuse of tendon tissue resulting in tendinopathy, which is characterized by pain during activity and significantly Impaired performance (1–4). Tendinopathy is often prolonged, and the pathogenesis behind tendinopathy is unclear. Heinemeijer 2018>>

<<Tendon disorders are mostly seen among people practicing sports, but can be observed also in the sedentary population. Genetic vulnerability, overuse, aging and metabolic disorders have been identified as risk factors that predispose to tendinopathies [Abatte 2009]. Abate in Ackermann 2016 Ch15>>



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1) Tendinopathy does not improve with rest – the pain may settle but returning to activity is often painful again because rest does nothing to increase the tolerance of the tendon to load.

2) Although there are some inflammatory biochemical and cells involved in tendinopathy, it is not considered to be a classic inflammatory response. Anti inflammatories may help if you have very high pain levels but it is unclear what effect they have on the actual cells and pathology.

3) Tendinopathy can be caused by many different risk factors. The main factor is a sudden change in certain activities – these activities include 1) those that require the tendon to store energy (i.e. walking, running, jumping), and 2) loads that compress the tendon. Some people are predisposed because of biomechanics (e.g. poor muscle capacity or endurance) or systemic factors (e.g. age, menopause, elevated cholesterol, increased susceptibility to pain, etc). Predisposed people may develop tendon pain with even subtle changes in their activity.

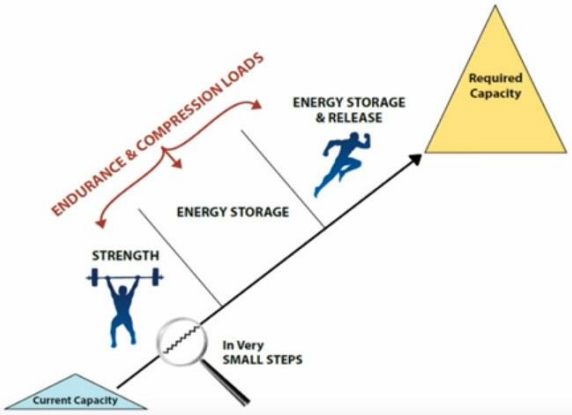
4) Exercise is the most evidence based treatment for tendinopathy – tendons need to be loaded progressively so that they can develop greater tolerance to the loads that an individual needs to endure in their day-to-day life. In a vast majority of cases (but not all) tendinopathy will not improve without this vital load stimulus.

5) Modifying load is important in settling tendon pain. This often involves reducing (at least in the short-term) abusive tendon load that involves energy storage and compression.
6) Pathology on imaging is NOT equal to pain – pathology is common in people without pain. Also, if you have been told you have 'severe pathology' or even 'tears' this DOES NOT necessarily mean you will not get better or have a poorer outcome. Further, we know that even with the best intentioned treatment (exercise, injections, etc) the pathology is not likely to reverse in most cases. Therefore, most treatments are targeted towards improving pain and function, rather than tissue healing, although this still is a consideration.
7) Tendinopathy rarely improves long term with only passive treatments such as massage, therapeutic ultrasound, injections, shock-wave therapy etc. Exercise is often the vital ingredient and passive treatments are adjuncts. Multiple injections in particular should be avoided, as this is often associated with a poorer outcome.
8) Exercise needs to be individualised. This is based on the individual's pain and function presentation. There should be progressive increase in load to enable restoration of goal function whilst respecting pain.
9) Tendinopathy responds very slowly to exercise. You need to have patience, ensure that exercise is correct and progressed appropriately, and try and resist the common temptation to accept 'short cuts' like injections and surgery. There are often no short cuts.
Please note that these are general principles and there are instances when adjuncts, including injections and surgery are very appropriate in the management of tendinopathy.
Dr Peter Malliaras - https://www.physio-network.com/9-tendinopathy-truths-you-must-know/ >>

<<Overview: Tendinopathies are frequent disorders best known for the Achilles and the patellar tendon. Tendinopathies are characterized by disorganization of the collagen matrix with an increase in ground substance, hypercellularity and vessel in-growth. In later stages, inflammation occurs mainly in surrounding tissues and at the insertions. Pain is related to inflammation and to changes in nociception. The first line treatment of tendinopathies is conservative for minimally three months, with specific progressive eccentric exercises being more successful than conventional rehabilitation approaches. Shockwave therapy, sclerosing injections and microsurgery may be used when eccentric exercise alone does not improve the condition. Ultimately, full-thickness excision of abnormal tissue followed by rehabilitation may be necessary. In this situation, eccentric exercise is seen as an important part of the rehabilitation programme. For epicondylalgia and tendinopathies of the rotator cuff and the tibialis posterior, the evidence for the value and appropriate modalities of eccentric exercise is scarce and equivocal.>>

How do we rehabilitate a tendon

- A staged loading program
  - First unload to settle pain and tendon
    - Decrease energy storage loads, frequency and volume and intensity of training
    - Add isometrics for pain and brain
  - Then gradually reload
    - To the level they need for their activity
      - Strength, energy storage and release loads
      - Add endurance and compression as needed



(Cook 2017)

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<<Cook - 2017 - https://www.youtube.com/watch?v=-kKzoi8Zrik>>

<<Exercise is the most evidence based treatment for tendinopathy – tendons need to be loaded progressively so that they can develop greater tolerance to the loads that an individual needs to endure in their day-to-day life. In a vast majority of cases (but not all) tendinopathy will not improve without this vital load stimulus.

Exercise needs to be individualised. This is based on the individual's pain and function presentation. There should be progressive increase in load to enable restoration of goal function whilst respecting pain.
Dr. Peter Malliaras blog Physio Network>>

Heavy slow resistance:

- Loads the tendon
- Increses muscle strength

Does not:

- Fully addresses kinetic chain and brain

- adapt the tendon to energy storage loads
- compressive loads

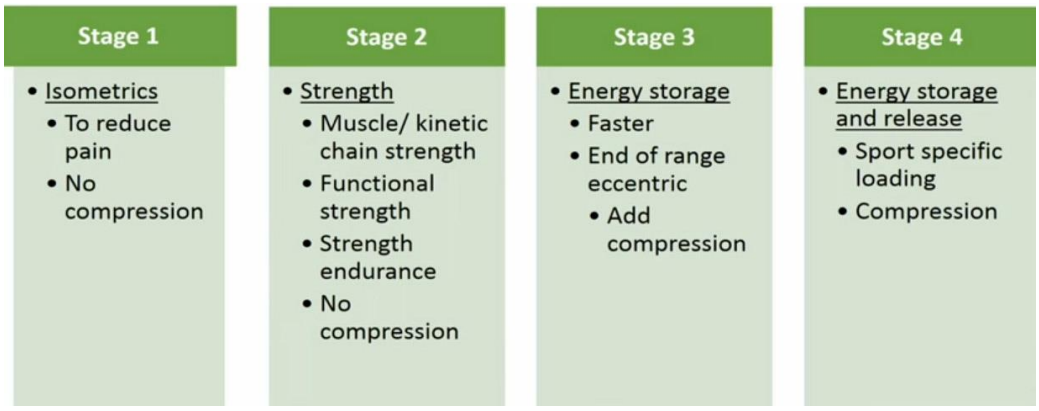
Eccentric:

- Loads the series elastic component

Does not:

- strengthen the muscle, kinetic chain or change the brain
- adapt the tendon to energy storage loads
- compressive loads

Four stages of rehabilitation



(Cook 2017)

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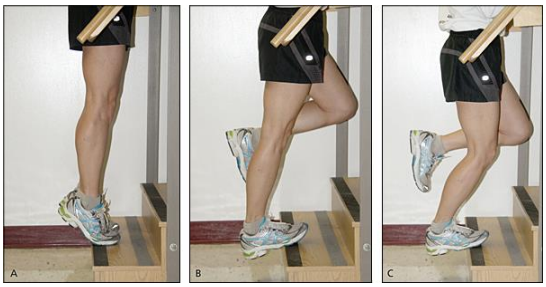
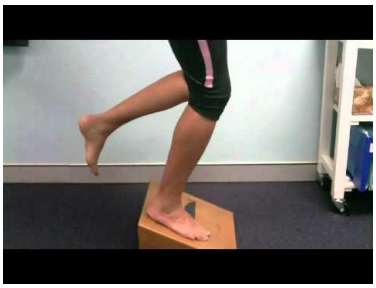
<<Cook - 2017 - https://www.youtube.com/watch?v=-kKzoi8Zrik>>

Excentrisch trainen?





Alfredson

- Zwaar en langzaam waarschijnlijk het beste voor peesadaptatie
- Excentrisch of concentrisch maakt niet uit

6

<<While most clinicians assumed that it is the eccentric contraction which is responsible for this effect, recent investigations from Kjaer et al. (2014) suggest that it is only the slow speed of the execution of the exercise that accounts for the beneficial results and not the eccentric or concentric activation
Gordon in Schleip 2015 H24>>

<<In addition, it should be noted that in a rat model it was demonstrated that the stimulatory effect upon collagen and IGF-I expression was similar whether the muscle contraction mode was of concentric, isometric or eccentric irrespective of the fact that the force-time integral was far greater for the eccentric contraction (Heinemeier et al., 2007a).

Although it is well known that the tendon cells (fibroblasts) respond to strain, the dose response to strain magnitude is not well established. Most (Webb et al., 2006; Joshi & Webb, 2008; Gauvin et al., 2011), but not all (Feng et al., 2006) studies have found that the adaptive response of fibroblasts to dynamic load is superior to that of static load. In healthy human Achilles tendons it has been shown hat exercising at 90% of MVC (~5% tendon strain) yield increased stiffness and cross-sectional area compared to working at 55% MVC (~3% tendon strain), and that the tendon was

more responsive to long duration (6s cycle) than a high faster loads (2s cycle) (Arampatzis et al., 2007; Arampatzis et al., 2010). Studies specifically addressing the effects of recovery and how it affects tendon adaptation are lacking.

Achilles tendon stretch is identical during the concentric and eccentric component of a heel rise/drop against body weight (Rees et al., 2008; Chaudhry et al., 2015). The cellular response to concentric or eccentric contraction to the same force level is similar with respect to the expression of collagen (Garma et al., 2007).

The 12-weeks of resistance training in healthy persons with either concentric or eccentric knee extensions produce a similar magnitude of tendon hypertrophy (Farup et al., 2014). These findings reinforce the notion that the cellular and tissue response in healthy tendon is independent on contraction mode.

Loading based interventions have become a principal theme in the treatment of tendinopathies (Malliaras et al., 2013), with positive clinical (Alfredson et al., 1996; Alfredson & Lorentzon, 2000; Mafi et al., 2001; Silbernagel et al., 2007), structural, and biochemical outcomes (Couppe et al.,
2009b; Kongsgaard et al., 2010). Isolated eccentric loading paradigm has mostly been regarded as the treatment of choice, although there is a lack of support for its superior effective (Malliaras et al., 2013). Other loading-based exercise regimes, including isolated concentric training (Mafi et al., 2001), heavy slow resistance training (Kongsgaard et al., 2009; Beyer et al., 2015) and concentric eccentric progressing to eccentric training (Silbernagel et al., 2001; Silbernagel et al., 2007) also appears to be clinically effective. To what extent a loading regime influences the tendon composition in patients with tendinopathy is very sparsely investigated. It has been shown that fibril morphology is abnormal in tendinopathy, but that heavy slow resistance training can change fibril morphology toward normal fibril density and mean fibril area (Kongsgaard et al., 2010). It has also been shown that the crosslink composition can be changed with heavy slow resistance training in this patient group (Kongsgaard et al., 2009).
Magnusson 2018>>

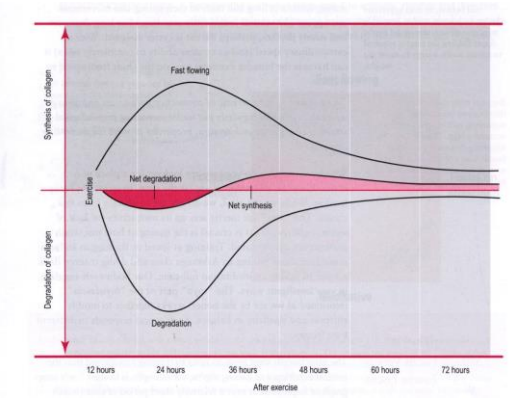
<<But what causes the connective tissue to cell remodel? Here, too, we know from the observations of strength training that the body responds to the smallest or smallest of injuries when it responds to the appropriate stimulus to exercise. The healing of the smallest injuries causes a cell reorganization. This can also lead to an increase in myofibroblasts (see Chap.lll.b.iii.3).
In the case of strength training, with the desire to increase the number of myofibroblasts, it is currently assumed that training intensities of> 60% of the individual strength make sense. It is likely that even acting forces of> 75% of the individual maximum force will be necessary to have an effect on the fibroblasts. It is

crucial that the acting forces cause the fibroblasts to deform, so that they are stimulated to synthesize. Slomka 2014>>

<<The detection of mechanical signals is key for tendon function given that their primary role is to transmit mechanical forces from muscle to bone to effect movement. Under normal physiologic conditions, tendons are subjected to low strains. At 1 % strain in whole tendon in vivo, the matrix crimp pattern is unaffected and cells are nominally deformed [Arnoczky 2002. However, an applied 3 % strain deforms collagen fibrils to a straightened position.
The tendon is taut and can undergo reversible deformation thus, the cells are subjected to a level of deformation above a nominal threshold. At strain, the tendon is subjected to the upper limit of elastic deformation and suffers some plastic deformation. Plastic deformation could include cell-cell contact disruptionor alterations in protein arrangement within the tenocyte plasma membrane, such as connexin 43 (Cx43)Jthe primary constituent of gap junction channels in tenocytes [McNeilly 1996] and initiate an inflammatory response that involves interleukins, MMPs, and insulin like growth factor [Scott 2007, Scott 2005, Speisz 2015, Sun 2008].
Wall in Ackermann 2016 Ch 7>>

Effecten training

- Toename collegeensynthese
  (alleen perifere deel van de pees bij volwassenen)
- Toename MMP's
- Voeding (fluid dynamics)



Ontstekingsremmers remmen collageensynthese!

Chronische ontsteking remt waarschijnlijk collageensynthese

7

<<On the degradation side it has been demonstrated that matrix metalloproteinase activity (MMP´s) is increased with exercise (Koskinen et al., 2004), and that the activation of ERK1/2 seems important for this MMP response (Sugg et al., 2017). Finally, the determination of breakdown products of collagen revealed a higher release of these in response to exercise and prolonged physical training (Langberg et al., 1999;
Langberg et al., 2001).

The role of inflammation for acute physiological changes in tendon has been investigated in several ways. It is demonstrated that inhibition of COX-2 specific pathways will abolish the exercise induced rise in tendon blood flow in humans (Langberg et al., 2003). Further, stretching of tendon cells has resulted in prostaglandin E2 release in a dose dependent manner (Wang et al., 2003; Legerlotz et al., 2013), and in humans the blockade of inflammation during acute exercise completely inhibited the rise in collagen synthesis normally seen in response to exercise (Christensen et al., 2011).

In bovine models tendon stretching has resulted in both rise in IL-6 and collagen type I mRNA (Legerlotz et al., 2013), and in humans a marked peritendinous rise in the

interstitial tissue concentration of IL-6 (and collagen synthesis) was found in association with exercise (Andersen et al., 2011), and
an infusion of IL-6 into the peritendinous tissue in the resting state caused a rise in collagen synthesis (Andersen et al., 2011). This suggests that a certain rise in inflammatory mediators is important for collagen turnover and for tendon adaptation to exercise. This mandatory increase in inflammatory parameters for activation of collagen synthesis may be independent upon the potential inhibiting effect upon collagen synthesis of a chronic elevated inflammatory state (e.g. in aging, disease or immobilization). In de-tensioning of tendon expression of collagen I is immediately reduced together with a rise in expression of inflammatory signaling markers (Bayer et al 2014).

In support of a comparable loading-induced tendon collagen synthesis in adult humans, microdialysis studies show increased levels of markers for collagen synthesis in the peritendinous tissue surrounding the Achilles tendon tissue, in response to both acute exercise and long-term training (Langberg et al., 1999; Langberg et al., 2001). However, these microdialysis data likely reflect the collagen synthesis at the very periphery of the tendon and might not completely reveal changes of the actual tendon tissue. Using stable isotope infusion with tendon biopsy sampling an increased rate of collagen synthesis was
observed in patellar tendons of young men in response to acute kicking exercise (Miller et al., 2005). However, several other studies using the same technique, and the same exercise model, could not in the same robust way confirm this loading-induced collagen synthesis in adult human tendon (Hansen et al., 2009a; Hansen et al., 2009b; Petersen et al., 2010; Dideriksen et al., 2013).

Studies have investigated gene expression in human patellar tendon tissue in response to acute exercise. In two of these investigations they found decreased or unchanged growth factor and collagen mRNA expression in tendon biopsies from the mid-portion of the tendon (Sullivan et al., 2009; Heinemeier et al., 2013a), while one study found modest increases in collagen and CTGF mRNA expression in tissue from the proximal part of the patellar tendon in response to exercise (Dideriksen et al., 2013). In other words, the response of adult human tendon tissue to acute loading does not seem to mimic that of rodent tendon tissue.
This suggests that adult human tendon tissue is far less responsive than that of small animals, and such differences may relate to the fact that rats and mice are still in a growth phase when they are typically used in experiments (typically at 10--12 weeks of age for rats) (Olesen et al., 2006; Heinemeier et al., 2007a; Heinemeier et al., 2007b). This hypothesis is supported by recent data on 6-month-old mice, which showed that overload-induced plantaris tendon hypertrophy was based on growth and cell proliferation only in the most superficial layers of tendon tissue, while the “original” core tendon remained relatively

constant (Gumucio et al., 2014). A greater potential for growth at the tendon periphery is further supported by an early study that showed greater levels of IGF-I protein expression in cells located in the rat Achilles tendon periphery compared to the more profund parts of the tendon (Hansson et al., 1988).
In other words, it may be speculated that a new layer of the collagen matrix is added in the periphery, analogous to that of a tree, when the tendon grows in response to loading. Magnusson 2018>>

<Neuronal Effects of Tendon Loading Physical activity has been demonstrated to accelerate the neuronal plasticity in tendon repair [Bring 2007]. It has moreover been demonstrated that exercise leads to increased levels of various neuromediators and their receptors, including SP and CGRP, which may be involved in regulating the healing response [Bring 2010, Ackermann 1999, Ackermann 2001]. Ackermann in Ackermann 2016 Ch 4>>

<< From a mechanical perspective, it can be observed, that shortly after strain in the Achilles and patella tendon, the tendon's cross-sectional area decreases significantly. In transverse strain, recovery was prolonged. The authors speculate that decrease of tendon diameter resembles a squeeze of water. The resulting rehydration in recovery may be an important contributor to a slow-acting exchange of nutrients, electrolytes and other humoral factors, such as cytokines (Wearing et al., 2013).
Klingler in Schleip 2015 Ch3>>

Tendons are certainly trainable. For athletes with a mainly one-sided load (tennis players, fencers, etc.), the tendons on the dominant are clearly thicker. Volleyball players have thicker Achilles tendons than rowers of the same level.
Training of tendon always depends on the strength of the muscle. You cannot load the tendon more heavily than the maximum isometric force of the muscle. This maximum force depends on the position

<<Mechanical stimuli can lead to tendon cell responses that can lead to changes of the extracellular matrix. Cell culture studies on tendon show that fibroblasts respond to mechanical stretch by increasing their production and secretion of certain growth factors that in turn act on the fibroblasts in an autocrine or paracrine fashion to induce expression and synthesis of collagen (Chiquet et al., 2009).

Thus, it seems likely that the tendon cells respond to loading by increasing growth factor production, and that the action of these growth factors leads to induction of collagen expression, although it remains to be proven.
Magnusson 2018>>

<<Finally, with regard to the development of the tissue, it must be presumed that a

mechanical strengthening of the tendon tissue will occur after the age of 13 yr via increased levels of mature crosslinks in the collagen matrix (25).
Heinemeier 2018>>

<< Tendon tissue belongs to the category of mechanically sensitive tissues that respond to mechanical stress by upregulating gene expression of collagen proteins. Proteins synthesis is reported to be co-regulated in muscle and tendon tissue, and peaks at 24 hours after stress, but remains elevated beyond 72 hours (Miller et al, 2005). This indicates a transcriptionally regulated stimulation of collagen synthesis similar to the transcriptionally regulated adaptations of skeletal muscle tissue with repetitive loads. On the other hand, collagen catabolism as a consequence of loading also occurs. The peak of collagen catabolism after repetitive loading is assumed to occur earlier than the peak of collagen synthesis (Maffulli et al, 2010). It has thus been hypothesized that too frequent (over)loading of tendons could lead to a negative collagen balance and to a long-term catabolic situation in tendon tissue (see Ackermann and Renstrom, 2012). There is evidence for inflammation, presence of macrophages, T cells and mast cells in early overload tendinopathy (Millar et al, 2010). It has further been suggested that tendon tissue hypoxia might play a key role in early tendinopathies driving the synthesis of proinflammatory cytokines and apoptosis (Millar et al, 2012). Vessel in-growth has also been attributed to hypoxia and concomitant upregulation of HlF-la, known to be a potent stimulator of VEGF (vascular endothelial growth factor). It is suggested that in-growth of nerves occurs together with, or subsequent to, vessel in-growth from the para- and epitenon (Messner et al, 1999). Changes to the status of the nociception in tendons are also discussed as important factors in later stage painful tendinopathy (Dean et al, 2013). In this context, presence of the neuropeptide substance P and increased pain-related glutaminergic signalling play major roles. Hopeler 2015>>

Problemen met oefenen

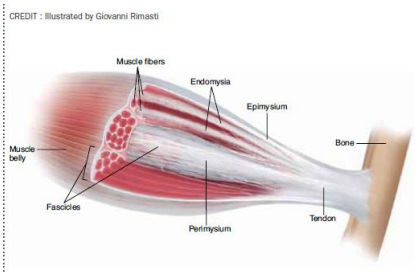
- Het is niet nieuw
- Veranderingen zijn langzaam
- Het is goedkoop

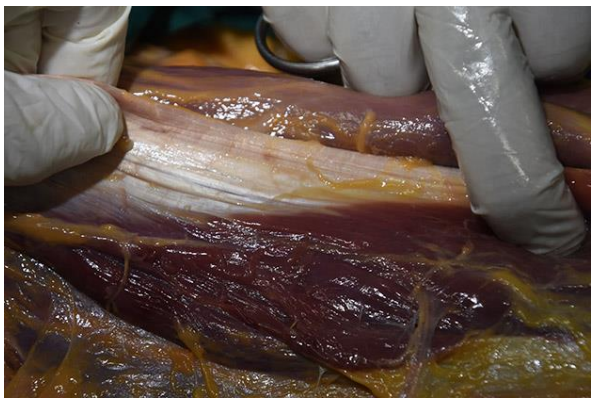
(Cook 2017)

8

<<Tendinopathy responds very slowly to exercise. You need to have patience, ensure that exercise is correct and progressed appropriately, and try and resist the common temptation to accept ‘short cuts’ like injections and surgery. There are often no short cuts. Dr. Peter Malliaras blog Physio Network>>

Pees is voortzetting van spierbindweefsel





Maar verzameling kokertjes met veel vocht er tussen

9

De pees - anatomie

55-70% water!

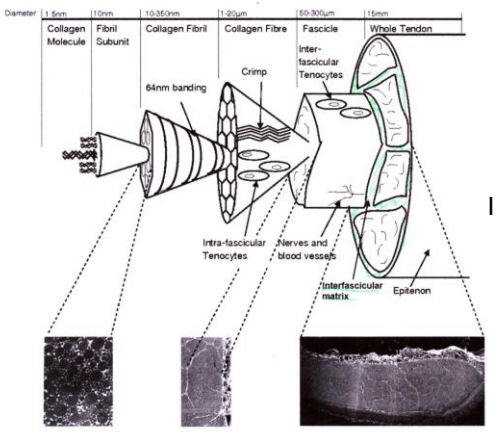


Fig. 1.1 Schematic showing the hierarchical structure of tendon, in which collagen molecules aggregate, forming subunits of increasing diameter (Adapted from Thorpe et al. [35] with kind permission from Wiley publishing)

IFM: interfascicular matrix

(Thorpe 2016)

10

<<Typical of connective tissues, tendon is predominantly composed of water, which makes up 55—70 % of total tendon weight. By far the majority of the tendon dry weight consists of collagens (60—85 %) [Kjaer 2004].

Collagen molecules within tendon are arranged in a hierarchical manner (Fig. 1.1) and at each level of the hierarchy, the collagen is interspersed with a less fibrous, highly hydrated matrix, traditionally referred to as the ground substance [Kastelic 1978, Thorpe 2013].

Collagen fibrils are stabilised by crosslinking, and the fibril is generally defined as the primary structural unit across many different tissue types. In tendon, fibrils aggregate to form collagen fibres, with the fibres aggregating once again to make up the largest subunit of tendon, the fascicle. Fascicles are visible to the naked eye, with diameters ranging from 150 to 500 microm. Each fascicle is surrounded by a connective tissue compartment called the interfascicular matrix (IFM). The IFM (sometimes also referred to as the endotenon) binds the fascicles to make the complete tendon unit, and is particularly important for tendons which function as energy stores [Thorpe 2012].
The tendon surface is covered by the epitenon, which is a connective tissue sheath

continuous with the IFM. An additional loose connective tissue layer, he paratenon , surrounds the tendons in regions away from joints, to facilitate movement of tendons below the skin. However, where a tendon passes around a joint, it is contained within a synovial sheath in order to ensure smooth gliding past surrounding structures.

Collagens
Type I collagen is the predominant collagen in tendon, making up approximately 90 % of the total collagen content [Birch 2007, Kjaer 2009]. Other fibrillar collagens are also present, including types Ill, V and XI. Collagen type Ill is the second most abundant tendon collagen, comprising up to 10 % of the collagen content. It plays an important role in collagen fibrillogenesis by regulating the size of type I collagen fibrils [14]. It is often localised to the IFM [Södersten 2013], but the role it plays in this tendon compartment is yet to be established. Type V collagen is found in the centre of collagen-I fibrils, where it is thought to provide a template for fibrillogenesis [Riley 2004].
Thorpe in Ackermann 2016>>

<<Previous studies have shown that the IFM has a distinct composition and greater cell density compared to fascicles [Thorpe 2016]. Fascicles consist of highly aligned collagen fibres interspersed with sparsely distributed elongated cells, whilst the IFM is more disorganised in appearance, with a greater number of more rounded cells, more collagen type III and proteoglycans (particularly lubricin), but a lower collagen type I content [Thorpe 2016, Kannus 2000, Fallon 2002]. Additionally, recent work suggests a greater rate of matrix turnover within the IFM, which may act to maintain healthy tendon structure [Thorpe 2016]. Godinho 2017>>

<<However, in a recent study used serial block face-scanning electron microscopy on tissue from adult human patellar and hamstring tendons, it was possible to track 2700 fibrils over a defined distance and only detect one single fibril tip (Svensson et al., 2017). Based on the data it was estimated that the fibril length was 67.5 mm, which strongly supports the notion that fibrils are continuous (Svensson et al., 2017). Magnusson 2018>>

<<Innervation of intact healthy tendons is localized in the surrounding structures, i.e paratenon, endotenon and epitenon, whereas the tendon proper is practically devoid of neuronal supply. This anatomical finding reflects that the tendon metabolism is regulated from the tendon envelope, i.e. interfascicular matrix

Tendon innervation after injury and during repair, however, is found as extensive nerve ingrowth into the tendon proper, followed by a timedependent emergence of different neuronal mediators, which amplify and fine-tune inflammatory and metabolic pathways in tendon regeneration. After healing nerve fibers retract to the

tendon envelope.
These observations of early nerve regeneration are in line with observations on bone, ligament and skin healing indicating that nerve ingrowth and subsequent retraction are _fundamental aspects of tissue repair [Hukkanen 1993, Kishimoto 1984 Li 2001, Martin 1997].
Ackermann in Ackermann 2016 Ch 4>>

<< Fibre composite materials stretch through a combination of extension of, and shearing between, the fibrous components.

The proportional contributions of fibre extension and shearing to total material stretch depend on the relative mechanical properties of the fibres and surrounding matrix. Alterations to local extension and shearing mechanics in a fibre composite can substantially affect the gross mechanical properties of the bulk tissue. With multiple hierarchical levels to tendon structure, there is significant scope for altering its local extension and sliding mechanics, and consequently whole tendon mechanical behaviour, through simple, often minor adjustments to composition at one or more of the tendon hierarchical levels. As such, understanding not just the overall composition of tendon, but also the organisation of matrix molecules throughout the tissue hierarchy is critical to understanding tendon function. Thorpe in Ackermann 2016>>

Verschillende typen pezen

Energy-storing tendons:
- Achilles pees
- Patellapees
- Psoas?
- Hamstrings?
- Ilio Tibial Band?

Positional tendons
- Extensoren voet/tenen
- Pezen bovenste extr.

Energy storing tendons
- Beter verlengbaar
- Elastischer (grotere crimp hoek, meer elastine)
- Minder vermoeibaar
- Minder collageen – meer water, meer lubricine
- Minder turn-over
- Fascicles meer helix structuur

11

<< Although the predominant function of all tendons is to transfer force from muscle to bone and position the limbs, some tendons additionally function as energy stores, reducing the energetic cost of locomotion. To maximise energy storage and return, energy-storing tendons need to be more extensible and elastic than tendons with a purely positional function. These properties are conferred in part by a specialisation of a specific compartment of the tendon, the interfascicular matrix, which enables sliding and recoil between adjacent fascicles.

Energy-storing tendons such as the human Achilles and patellar tendons have an important role in reducing the energetic cost of locomotion by stretching and recoiling with each stride to store and return energy (Lichtwark & Wilson, 2005; Malliaras et al. 2015).

It has been shown that the collagen crosslink profile and collagen fibril diameter differ in energy-storing and positional tendons (Birch et al. 2006; Birch, 2007).

It has also been demonstrated that fascicle structure differs between tendon types, with the presence of a helical component in fascicles from energy-storing tendons which enables increased elasticity (Thorpe et al. 2013b).

Other studies have also shown that the IFM is rich in lubricin (also known as superficial zone, or proteoglycan-4) (Funakoshi et al. 2008; Sun et al. 2015) and elastin (Smith et al. 2011; Grant et al. 2013).

It has been demonstrated that a reduction in lubricin content reduces tendon and fascicle gliding ability (Taguchi et al. 2009; Kohrs et al. 2011), suggesting that the function of this glycoprotein in the IFM may be to facilitate sliding between fascicles. This is particularly important in energy-storing tendons, where the greater requirement for extension appears to be provided by a larger degree of interfascicular sliding (Thorpe et al. 2012). Thorpe 2016>>

<< Fibre composite materials stretch through a combination of extension of, and shearing between, the fibrous components.

The proportional contributions of fibre extension and shearing to total material stretch depend on the relative mechanical properties of the fibres and surrounding matrix. Alterations to local extension and shearing mechanics in a fibre composite can substantially affect the gross mechanical properties of the bulk tissue. With multiple hierarchical levels to tendon structure, there is significant scope for altering its local extension and sliding mechanics, and consequently whole tendon mechanical behaviour, through simple, often minor adjustments to composition at one or more of the tendon hierarchical levels. As such, understanding not just the overall composition of tendon, but also the organisation of matrix molecules throughout the tissue hierarchy is critical to understanding tendon function.

Elastic fibres are also found in varying amounts throughout the tendon matrix, with reported concentrations from 1 to 10 % of tendon dry weight. These fibres are predominantly localised to the IFM (Fig. 1.2) but are also present within fascicles, particularly around cells [Grant 2013]. Elastic fibres have a central core of elastin, which is surrounded by a sheath of fibrillins 1 and 2, as well as other associated proteins [Kielty 2002]. Elastic fibres are highly elastic, fatigue resistant and able to store and return energy [Thorpe 2013]. In ligament, elastin resists transverse and shear deformation [Henniger 2015], but it is yet to be established whether it has a similar role in tendon.

In man, the predominant energy storing tendons are the Achilles and patellar tendons. In order to store and return energy effectively, energy storing tendons require specific mechanical properties, including increased extensibility, elasticity and fatigue resistance. These specialised properties are conferred by alterations in matrix structure and composition, targeting different levels of the tendon fibre composite hierarchy.

Variation in Tendon Collagen

Variations in collagen content and organisation between energy storing and other (positional) tendons are seen throughout the hierarchy. Energy storing tendons have a lower total collagen content than positional tendons [Thorpe 2010]. How ever, type II collagen levels are elevated in energy storing tendons [Thorpe 2015]. Type Ill collagen is abundant in tissues that require a high degree of compliance, such as skin and blood vessels, and therefore the higher levels in energy storing tendons may provide the greater extensibility and improved recoil needed in this tendon type. Collagen crosslink profile also differs between tendon types. Such differences in crosslinking are likely to influence fibril stiffness and subsequent local mechanics throughout the tendon hierarchy. However, the influence of crosslink type on tendon mechanical properties is yet to be determined [Birch 2007]. Differences are also seen at the fibril level; fibrils in energy storing tendons have a bimodal distribution, with a lower mass average fibril diameter, which may contribute to the increased compliance in this tendon type. In addition, collagen crimp angles are greater in energy storing tendons [Thorpe 2013], which may provide greater energy storing capacity. Differences in collagen packing are also seen at the fascicular level; fascicles from energy storing tendons have a smaller diameter than those from positional tendons. Collagen turnover rate also varies with tendon type, with lower levels of collagen turnover in energy storing tendons resulting in an extremely long half-life of approximately 200 years [Thorpe 2010].

Variation in Non-collagenous Components

There are also several variations seen in the abundance of non-collagenous matrix components between tendons with different functions. Levels of sulphated glycosaminoglycans are significantly higher in energy storing tendons than in positional tendons [Thorpe 2010], indicative of increased total proteoglycan levels in these tendons. Correspondingly, energy storing tendons have an evated water content, which is negatively correlated with tissue stiffness [Birch 2007].

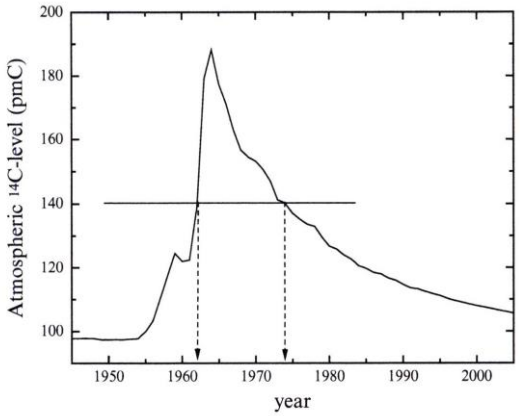
Mechanical testing studies indicate that sliding between adjacent fascicles is the primary mechanism by which energy storing tendons are able to stretch and recoil efficiently [Thorpe 2012]. To achieve this, the IFM in this tendon type must be highly specialised to facilitate low stiffness inter-fascicle sliding and elastic recoil. Recent studies have started to elucidate the structural and compositional IFM specialisations in energy storing tendons that confer these mechanical properties. It is apparent that there are differences in IFM content between tendon types, with a larger volume of interfascicular matrix in energy storing tendons [Thorpe 2013]. In addition a very recent study has compared the distribution of proteins within the IFM and fascicular regions of energy storing and positional tendons, demonstrating enrichment of lubricin and elastin in the IFM, which is particularly pronounced in energy -storing

tendons. [Thorpe 2016]. Based on the properties of these proteins, it is likely that lubricin facilitates inter-fascicular sliding, whereas elastin enables efficient recoil of the IFM.

Age Related Changes to Matrix Turnover Rate

In general, protein synthesis in tissues decreases with advancing age [Travermarakis 2008], and therefore it might be expected that extracellular matrix proteins in tendon are renewed less often. Thorpe in Ackermann 2016>>

Peesadaptatie



(Heinemeier 2016)

Kern Achillespees na 17e jaar geen turn-over meer

12

<<Achilles tendons are developed steadily during the first 13 yr of life and not renewed after this age (Fig. 5A). (Heinemeier 2013)

Finally, with regard to the development of the tissue, it must be presumed that a mechanical strengthening of the tendon tissue will occur after the age of 13 yr via increased levels of mature crosslinks in the collagen matrix (Bailey A 2002). Heinemeier 2018>>

<< Some of these studies indicated a relatively fast turnover of the tendon collagen tissue (Langberg et al., 1999). Some studies in humans have found relatively high collagen synthesis rates in tendons of ~1% pr 24 hrs (Miller et al., 2005) while others have found more moderate values of around 0.2% pr 24 hrs (de Boer et al., 2007b; Nielsen et al., 2014).

The human Achilles tendon can be considered a high strain and injury prone tendon, and data obtained using the bomb pulse method indicates that the collagen structure of the core of the human Achilles tendon is changing until about the age of 17 yrs and thereafter the tissue structure is stable (Heinemeier et al., 2013b)

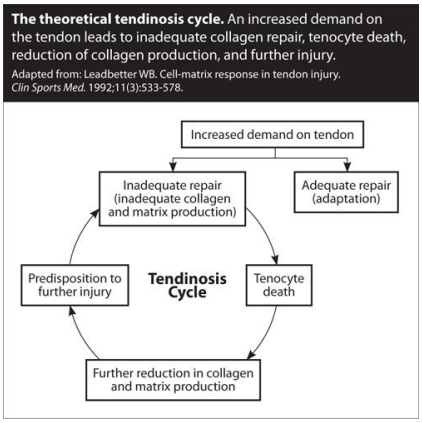
This leaves us with a challenge regarding the understanding of tendon tissue turnover in human tendons. It is suggested that the tendon collagen tissue consists of 2 pools of tissue, one that is relatively stable with relatively dormant cells where tissue is formed during childhood and adolescence, and one much smaller pool with a fast turnover where cells exert a kind of “daily maintenance” in order to maintain tissue homeostasis. Theoretically, such a model could fit to all available methodologies, and fits with the view that a major part of the tendon is developed during childhood and adolescence, and still at the same time allows for a daily adjustment and thus ability to adapt to changes in mechanical loading patterns. Presently, the anatomical locations of the proposed pools of tissue remain an enigma. Magnusson 2018>>

<<Opposing this, more recent studies on humans indicated a surprisingly high collagen turnover in tendon tissue with levels corresponding to the turnover of muscle contractile protein (0.045 % [h) [Miller 2005, Babraj 2005]. However, the measure of short-term incorporation of labeled amino acids suffers from the complication that it registers synthesis of all new collagen even though this newly synthesized collagen may often be rapidly degraded, and thus never incorporated into the tissue [McAnulty 1987].

Both strength training and habitual loading of tendons appear to be associated with an increase in tendon size [Kongsgaard 2005, Kongsgaard 2007, Couppe 2008, Arampatzis 2007], suggesting that the responses to elevated loading results in a net increase of tendon tissue. Heinemeier in Ackermann 2016 Ch 8>>

<<Data from horses show that high strain-injury prone tendons have slower turnover than low strain rarely injured tendons (Thorpe et al., 2010). Albeit counterintuitive, it may be that high-strain tendons simply cannot “afford” to have a constant ongoing remodeling as this may reduce the tendon strength. Therefore, the high-strain Achilles tendon may well have slower turnover than tendons that are loaded less, such as the patellar tendon. Magnusson 2018>>

Tendinosis in plaats van Tendinitis

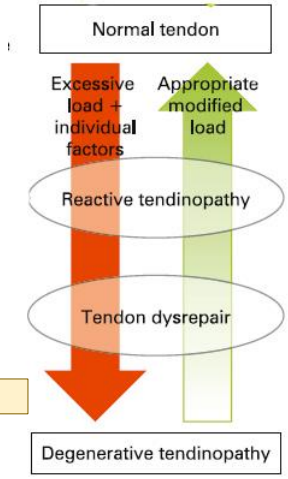


The theoretical tendinosis cycle. An increased demand on the tendon leads to inadequate collagen repair, tenocyte death, reduction of collagen production, and further injury.
Adapted from: Leadbetter WB. Cell-matrix response in tendon injury. *Clin Sports Med.* 1992;11(3):533-578.

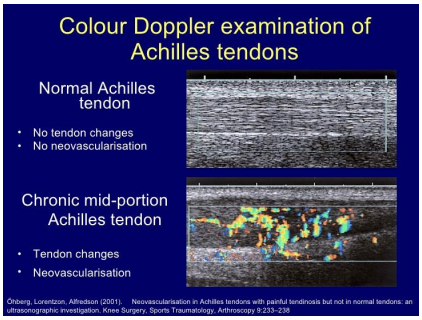
- Increase groundsubstance in tendon
- Ingrowth bloodvessels with free nerve endings
- Disorganised collagen
- Immature fibroblasts
- No imflammation cells

13

Relatie structuurveranderingen – pijn?



Model van Cook



14

<<Cook - 2017 - https://www.youtube.com/watch?v=-kKzoi8Zrik>>

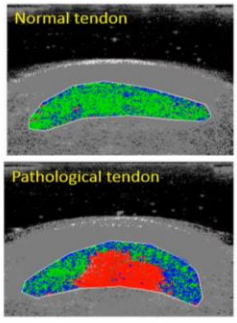
peespathologie

Do we need to change structure?

Treat the doughnut not the hole

Toch belastbaar!

	Normal	Pathological
Achilles tendon		
AP diameter (mm)	6.5 ± 0.5	8.4 ± 1.5
mCSA of poor structure(mm²)	1.4 ± 1.4	4.7 ± 8.3
mCSA of good structure (mm²)	80.8 ± 15.8	94.8 ± 26.5
Patellar tendon		
AP diameter (mm)	6.0 ± 0.6	7.8 ± 2.6
mCSA of poor structure (mm²)	4.5 ± 3.4	17.1 ± 22.3
mCSA of good structure (mm²)	125.9 ± 11.7	139.9 ± 23.1



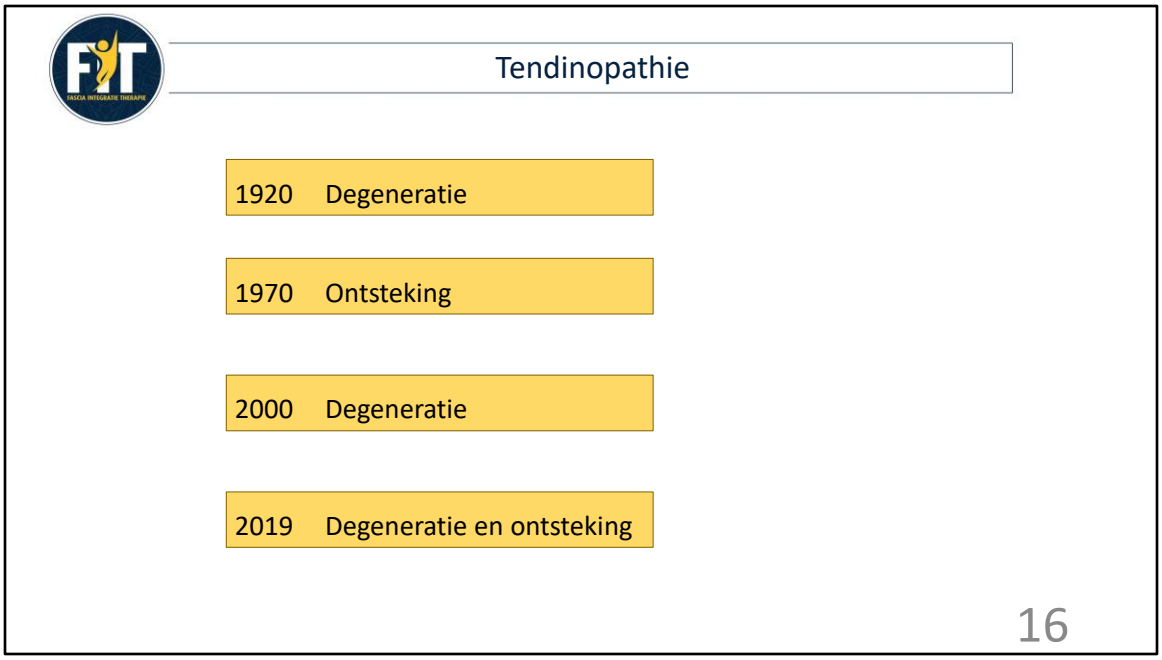
Docking and Cook 15

15

<<Cook - 2017 - https://www.youtube.com/watch?v=-kKzoi8Zrik>>

A degenerated tendon does not return to normal structure
Tendon pain causes profound dysfunction

<<Pathology on imaging is NOT equal to pain – pathology is common in people without pain. Also, if you have been told you have 'severe pathology' or even 'tears' this DOES NOT necessarily mean you will not get better or have a poorer outcome. Further, we know that even with the best intentioned treatment (exercise, injections, etc) the pathology is not likely to reverse in most cases. Therefore, most treatments are targeted towards improving pain and function, rather than tissue healing, although this still is a consideration.
Dr. Peter Malliaras blog Physio Network>>



<<It is known that tendinopathic (and painfull) tendon areas are associated with more rounded fibroblasts and cell accumulation (Glazebrook et al., 2008; de Mos et al., 2009).
Further there is an upregulation of mRNA for collagen I and II plus TGF-beta (Pingel et al., 2013a; Pingel et al., 2014), and increased amounts of proteoglycans, and of the proteins versican, aggrecan and fibromodulin, whereas decorin that normally is associated with aligned tendon fibrils was unchanged in its content in tendinpathic tendons (Parkinson et al., 2010). To what extend tendinopathy is associated with inflammation is still debated, but in general long term chronic tendinopathy is not dominated by inflammation, whereas different indicators of inflammation have been demonstrated early in tendinopathy (Dakin et al., 2015).

Structural & mechanical aspects
In addition to rounding of fibroblasts, increased cell number, an increase in the content of
proteoglycans glycosaminoglycans (GAGs), water, and hyper-vascularization (with nerve ingrowth), the collagen fibrils appear disorganized (Glazebrook et al., 2008; Kongsgaard et al., 2009; Pingel et al., 2013b). The increase in water content along with the hypervascularization leaves the tendon with an overall increase in CSA.

Tendon stiffness has been reported to decrease with tendinopathy (Arya & Kulig, 2010; Child et al., 2010; Helland et al., 2013), or remain unchanged (Kongsgaard et al., 2010). It remains unknown if such a change relates to the pathology itself or if it is an injury related inactivity (unloading) response. Magnusson 2018>>

<<There are indications of increased formation of collagen in tendons affected by long-term tendinopathy. These include increased mRNA expression of collagen types I and III (11–13) and increased cell number and cell rounding, as well as collagen disorganization.
In addition, variations in the accumulation of advanced glycation end products (AGEs) and D-aspartic acid between healthy and tendinopathic tendons support that newly formed collagen has been added to the diseased tendon (12–16).

In summary, the [14C] data indicate that tendinopathy leads to increased collagen turnover in 1 part of the tendon matrix,while another part remains stable. This results in a tissue containing both new and very old collagen.
In summary, our model suggests that the tendinopathic collagen matrix contains an old part that behaves similarly to healthy tendon (with no turnover in adult life) and a relatively new part that has an age of about 15 yr (indicating continuous but slow turnover).

This finding suggests that either the disease process has been ongoing for years before clinical symptoms occur or that a high matrix turnover is a risk factor, and perhaps a prerequisite, for the development of tendinopathy. Heinemeier 2018>>

<<Furthermore, the reader should refer to texts on the increasing understanding of inflammation in osteoarthritis, another condition previously considered to be 'degenerative' in nature. Speed in Ackermann 2016 Ch 20>>

Tendinopathie - predispositie

- Immobilisatie
- Veroudering
- Obesitas
  - gewicht
  - laaggradige ontsteking
- Diabetes mellitus
- Medicijnen

- Hypercholestorolemie
- Hyperuricemia
- Hypothyroïdie
- Geslachtshormonen
- Genetische factoren

17

Immobilisatie

2 weken immobilisatie:
- 80% minder collageensynthese
- Vermindering goede cross-links
- Meer MMP's

Connective Tissue Adaption to Mechanical Load

Inadequate (Disuse/immobilization)	Overload (Re-mobilization)	Excess Overload (Overuse)
Loss of ground substance Water Loss ⇓ inter-fiber distance ⇓ collagen fiber bundle size ⇑ cross-linking between existing collagen ⇓ inter-fiber mobility Collagen disorganization Eventual net collagen loss Insertion site weakening ⇓ structural properties ⇓ mobility	Cell proliferation & activity ⇑ collagen production ⇑matrix organization ⇑ ground substance ⇑ inter-fiber distance ⇑ blood flow ⇑ skin temperature ⇑ tissue extensibility Release of adhesions ⇓ muscle tone ⇑ structural properties ⇑ mobility	⇑ tissue strain → cell death Inflammation Degeneration Fibrosis

18

<<Here, the fibres proliferate and take on an irregular arrangement. Animal experiments have shown that immobilisation quickly leads to a dysregulation in fibre arrangement and to a multidirecfional growth of additional crosslinks between dense collagen fibres. As a result, the fibres lose their elasticity as well as the smooth gliding motion against one another. They then stick together forming tissue adhesions over time and, at worst, they become matted together (Jarvinen et al.,2002). Schleip in Schleip 2015 H1>>

<< When subjected to inactivity, the connective tissue doesn't diminish quickly in size, but does demonstrate a quick (within 1-2 weeks) alteration in passive mechanical properties. The explanation for this is currently unknown but indicates that molecular structures, that are of importance for mechanical properties, can change quickly when unloaded. In artificial tendons it has been shown that just a few days of unloading in tendonlike structures results in a disorganisation of the fibrils. In humans, the quick changes in mechanical properties of the tendon is accompanied by a change in the expression of enzymes of importance for the formation of crosslink molecules Kjaer in Schleip 2015 H5>>

<< Conversely, with inactivity over 2-3 weeks it can be shown that such incorporation

would be diminished. It therefore seems that the collagen production in tendon and skeletal muscle matrix is affected by the degree of mechanical loading. Interestingly, both in tendon and muscle it seems that the dose-response curve for the relation between intensity of loading and the responding protein synthesis outcome is leveling off relatively early. This means that, already at a relatively moderate loading of the tissue, a sufficient connective tissue response is observed. As adaptation of connective tissue in general is relatively slow, it presents an advantage that also relatively moderate loading will result in an increase in protein synthesis. Kjaer in Schleip 2015 Ch5>>

<< How much is considered to be adequate loading of connective tissue and how much is too much is an important but, as yet, unresolved question. We do know that appropriate restitution between training bouts will contribute to allow full stimulation of protein synthesis and protein degradation, in order to avoid a gradual net loss of connective tissue over time Kjaer in Schleip 2015 Ch5>>

<< Cellular & molecular aspect De-tensioning of tissue removes the constant signal for mechanotransduction in tendon. In tendon constructs made from human tenocytes it has been demonstrated that already a few days after removing tensile loading there is a down regulation of mRNA for both tenomodulin and collagen, and this is accompanied by a disorganization of the aligned fibrils in the tendon structure (Bayer et al., 2014).

These early studies indicated that loading of tendon is important for maintenance of matrix protein synthesis, and indirectly suggested that a certain magnitude of loading is needed to obtain an increase in matrix protein synthesis in tendon.

Creating tendon-like structures: Interestingly, the relation between loading and signaling for collagen synthesis was studied and based on the phosphorylation of ERK1/2 it was suggested that 10 min of 2.5 % stretch every 6 hrs was most favorable for improving tendon (Paxton et al., 2012).

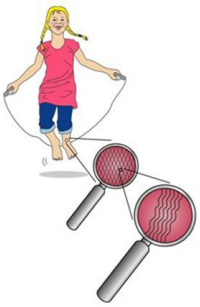
but already 2--3 weeks of immobilization of a lower limb in both young and old individuals will lead to a 80% reduction in synthesis rate of collagen (de Boer et al., 2007b; Dideriksen et al., 2017). In line with these changes, 2 weeks of immobilization resulted in a down regulation of LOX and scleraxis and an upregulation of MMP2 in human patella tendon (Boesen et al., 2013; Dideriksen, 2014).

The effects of immobilization on the tendon have been studied in animal models, and they overwhelming show a decline in mechanical properties (Woo et al., 1982; Yamamoto et al., 1993; Hannafin et al., 1995; Almeida-Silveira et al., 2000; Matsumoto et al., 2003; Rumian et al., 2009). It seems that the human data on the

effects of immobilization on tendon properties largely mirror those of the animal models (Reeves et al., 2005; de Boer et al., 2007a; Seynnes et al., 2008; Shin et al., 2008; Kinugasa et al., 2010; Couppe et al., 2012). Interestingly, it looks like rather short-term (1-2 weeks) limb unloading can significantly reduce the stiffness of the tendon. Moreover, the changes in mechanical properties take place in the absence of any change in cross-section of the tendon (Reeves et al., 2005; de Boer et al., 2007a; Christensen et al., 2008; Shin et al., 2008; Couppe et al., 2012). In fact, it appears that the cross-section of tendon will only be reduced during extremely protracted periods of inactivity (Maganaris et al., 2006). The mechanism for this relatively rapid change in mechanical properties in the absence of an overall change in the (MRI determined) size of the structure is elusive, but may relate to LOX derived cross-links. Magnusson 2018>>

<<Prolonged unloading may additionally be detrimental for the human tendon. Disuse leads to reduced tendon mechanical stiffness [Reeves 2003]. Prolonged unloading post injury also demonstrated negative effects on tendon mechanical properties and production of extracellular matrix molecules [Schizas 2010, Bring 2009, Bring 2009b]. Ackermann in Ackermann 2016 Ch 4>>

Veroudering / inactiviteit



- Genetische downregulatie matrix remodelering
- Vezels afgevlakt (loss of crimp and springiness)
- Disorganisatie
- Degradatie elastine
- Afname doorbloeding
- Maar geen afname totaal collageen / CSA

19

<< The effect of ageing is challenging to study because it is hard to separate age per se from the related inactivity associated with ageing (Lazarus & Harridge, 2017).
It was recently shown that old person (66 years) had a lower modulus compared to young persons (26 years), but when old and young were matched for activity level, there was no difference in mechanical properties (Couppe et al., 2014).

In regards to expression and synthesis of proteins from tendon cells, it has been shown that older rats demonstrated a reduced mRNA expression of collagen (I, III and V) whereas the protein content of collagen types estimated by immunohistochemistry was unchanged by ageing (Goh et al., 2008; Dyment & Galloway, 2015; Zhang et al., 2016). Further, decreased expression of elastin has been found with ageing whereas unchanged expression of the factors involved in tissue growth (CTGF and TGF-beta) was demonstrated with aging in rats (Kostrominova & Brooks, 2013).

In a recent study with young and old rats it was demonstrated that aging was associated with
a down regulation of genes that regulate matrix remodeling (Marqueti et al., 2018). Further, aged rats show a reduced density of blood vessels and a few examples of

calcification in older tendons were shown (Marqueti et al., 2018). Interestingly, the intervention with regular strength training in older rats upregulated mRNA expression of CTGF, decorin and VEGF, and no calcifications were found in tendons of old trained rats (Marqueti et al., 2018). Although the study found differences between young and old rats it also demonstrated that physical training can counteract several agerelated changes in tendon connective tissue, which is similar to that found in relation to aging and oxidative and metabolic capacity in skeletal muscle (Larsen et al., 2012).

cross-sectional studies in humans indicate that tendon CSA may increase (Magnusson et al., 2003; Stenroth et al., 2012; Couppe et al., 2014) or remain unchanged (Carroll et al., 2008; Couppe et al., 2009a; Couppe et al., 2014) with aging. However, not accounting for
reduced physical activity with aging (Lazarus & Harridge, 2017) and its potential effects on tendon CSA may be a key limitation. It was recently shown that young and old men of similar height, weight and activity level also displayed similar tendon CSA (Couppe et al., 2014), which suggests that unlike muscle there is no loss of tendon tissue with increasing age. In support of this, the total content of collagen fibrils (volume fraction) remains largely unaltered with aging in animals and humans models (Parry & Craig, 1978; Wood et al., 2011; Couppe et al., 2014). Magnusson 2018>>

<<Tendon is composed of fascicles bound together by the interfascicular matrix (IFM). Energy storing tendons are more elastic and extensible than positional tendons; behaviour provided by specialisation of the IFM to enable repeated interfascicular sliding and recoil. With ageing, the IFM becomes stiffer and less fatigue resistant, potentially explaining why older tendons become more injury-prone. We hypothesised that elastin is more prevalent in energy storing than positional tendons, and is mainly localised to the IFM.
Further, we hypothesised that elastin becomes disorganised and fragmented, and decreases in amount with ageing, especially in energy storing tendons. Biochemical analyses and immunohistochemical techniques were used to determine elastin content and organisation, in young and old equine energy storing and positional tendons. Supporting the hypothesis, elastin localises to the IFM of energy storing tendons, reducing in quantity and becoming more disorganised with ageing. These changes may contribute to the increased injury risk in aged energy storing tendons. Full understanding of the processes leading to loss of elastin and its disorganisation with ageing may aid in the development of treatments to prevent age related tendinopathy. Godinho 2017>>

<<Taking a closer look into the microstructure of the collagen fibres, it shows undulations, called crimp, which is reminiscent of elastic springs. In older people, or those whose fascial fibres suffer immobilisation, the structure of the fibre appears rather flattened, losing both crimp and springiness (Staubesand et al., 1997).

Research has confirmed the previously optimistic assumption that proper exercise loading of the fibres, if applied regularly, can induce a more youthful collagen architecture. This regains a more wavy fibre arrangement (Wood 1988, Larniven 2002), and expresses a significantly increased elastic storage capacity (Reeves 2006, Witvrouw 2007). Schleip in Schleip 2015 H1>>

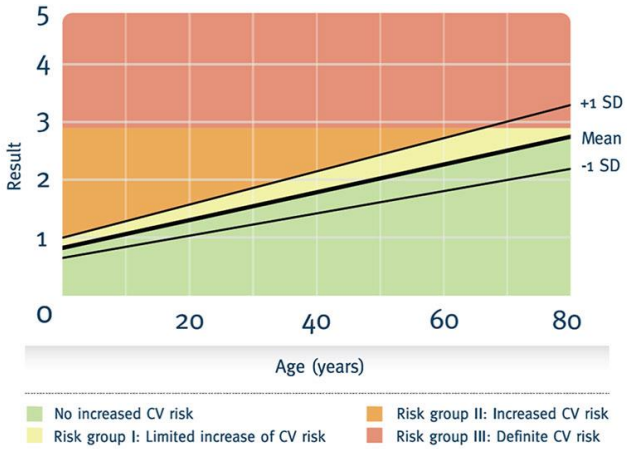
<<Tendon functional competence and structural integrity rely on homeostasis of tendon cell metabolism and extracellular matrix macromolecules. The clear link between tendinopathies and increasing age suggests a slow change to tendon homeostasis, which increases susceptibility to damage. Despite this well evidenced association between increasing age and tendon damage, changes to tendon mechanical properties with ageing are not clear with different studies reporting conflicting results. More recent research suggests that age-related changes occur at specific sub-structure locations and may be overlooked by measuring properties of the whole tendon. In this chapter we review changes to tendon mechanical properties, structure and composition. Mechanisms speculated to contribute to tendon change with age such as cellular senescence, ageing stem cell population, reactive oxygen species and formation of advanced glycation end-product crosslinks are discussed. Understanding age-related changes to tendon homeostasis are key to understanding increased incidence of tendon injuries in the ageing population.

In addition, other mechanical properties less often considered such as hysteresis and fatigue properties are likely to be very relevant with regard to tendinopathies. These properties are particularly important in the human patellar and Achilles tendon and the equine SDFT as they are subjected to a high number of loading and unloading cycles and function as elastic energy stores. Although quantifying hysteresis in vivo is problematic [Lichtwark 2013], a study of the tendonaponeurosis of the vastus lateralis showed an increase in hysteresis with ageing in a group of women between 21 and 77 years [Kubo 2003]. Hysteresis and post-loading recovery have been studied in fascicles from equine tendons in vitro and differences have been observed between tendon types and with ageing. Fascicles from the energy storing SDFT have lower hysteresis and a greater ability to recover after loading compared to those from the CDET. This difference can be explained by a difference in the extension mechanism; SDFT fascicles appear to extend by rotation of a helical structure while CDET fascicle extension is dominated by sliding of the component fibres [Thorpe 2013]. In older horses, the ability of the fascicles from the SDFT to recover following loading is reduced and hysteresis increases [Thorpe 2013]. Fatigue loading of SDFT fascicles in vitro results in changes similar to those seen in ageing; in fascicles from young horses rotation decreases and in fascicles from older horses where the helical structure is already compromised there is an increase in fibre sliding following fatigue loading [Thorpe 2014]. The inter-fascicular matrix in the SDFT, in addition to an increase in stiffness with ageing, also shows less ability to resist repetitive loading

[Thorpe 2015]. These studies demonstrate that the mechanical behavior of tendons is complex, as are the changes associated with ageing. Birch in Ackermann 2016 Ch 24>>

AGE-ing / Inflammaging

AGE related cross-links



20

<< Collectively, the data suggest that with age there is no change or a decrease in the modulus of the tendon. What is somewhat puzzling about these findings is that there is an increase in AGE's with age (Couppe et al., 2009b; Hansen et al., 2010; Couppe et al., 2014), which can be mitigated by physical activity (Couppe et al., 2014), and an elevation of AGE's would typically increase tendon stiffness (Bai et al., 1992; Li et al., 2013; Svensson et al., 2018). It is unclear, but it is possible that the increase in AGEs is partly countered by a reduction in collagen content with age (Couppe et al., 2009b). Magnusson 2018>>

<<Among the many factors playing a role in tendon disease, unregulated biochemical reactions between glucose and the collagen extracellular matrix are coming increasingly into focus. We have shown that formation of advanced glycation end-products that cross-link the collagen extracellular matrix can drastically affect cellular level mechanical properties of the matrix, and in turn affect cell-level biomechanical stimuli during physiological loading of the tissue. We suggest that these may adversely affect tendon cell response to matrix damage, as well as the quality of the consequent repair. If such mechanical feedback loops are altered, the ability of tendon cells to maintain tissue in a functional, healthy state may be compromised. Although key foundational elements of biochemical, biomechanical, and biological

understanding are now in place, the full extent of how these aspects interact, including the precise mechanisms by which advanced glycation end-products pathologically disrupt connective tissue homeostasis and damage repair, are only beginning to be adequately appreciated.

The so-callaed “Maillard reaction, also known as “glycation”or “protein browning” has been linked to the clinically observed stiffening of connective tissue [Avery 2006, Fu 1994, Monnier 1988, Sell 2012]. This process is a progressive and apparently irreversible feature of aging [Monnier 2005]. Extracellular matrix glycation is greatly accelerated in diabetes mellitus.

Tendon must withstand occasionally enormous mechanical forces, and yet transfers these forces within tightly constrained anatomical spaces. This delicate balancing act requires that the extracellular matrix be finely tuned in its basic material properties namely its elasticity, viscoelasticity, and resistance to mechanical damage. These tissue-level functions fundamentally rely on cell-mediated self-assembly of collagen molecules into functional building blocks that are known as collagen "fibrils". The physical properties of individual collagen fibrils is mostly dependent on collagen molecular packing and inter-molecular. cross-links [Depalle 2015].

It is thus at the cell-fiber interface that collagen glycation can be expected to directly provoke disruption of normal tendon tissue homeostasis [Li 2013]. Snedeker in Ackermann 2016 Ch 18>>

<<The authors concluded: "If tendinopathy is confirmed to be associated with dyslipidemia and the metabolic syndrome in larger studies, it may be appropriate to redefine our concept of tendinopathy to that of a cardiovascular disease (CVD). In this case, we may be able to draw considerably on CVD research to improve our understanding of tendinopathy, and perhaps treating CVD risk factors will improve the treatment of tendinopathy.“ Knoblauch in Ackermann 2016 Ch 22>>

<< Cellular Senescence
Cellular senescence, the irreversibly arrest of cellular division is an intricate biological process causing alterations in the protein expression profile of the cell and resulting in replicative arrest, changes in metabolism, adhesion efficiency and secretory phenotype [Hwang 2009]. Several of these modifications produce beneficial tumoursuppressive effects as they diminish the proliferation capacity of mutated cells. However, senescent cells are characterised by an increase in the secretion of growth factors, inflammatory cytokines, and proteases; the 'senescence’ associated secretory phenotype' (SASP), that can exert the opposite activity by creating a tumour-favoring milieu [Hwang 2009]. We can distinguish ageing from senescence by noting that the latter occurs at a cellular level [Sethe 2006].

Inflammageing

Inflammageing is considered the age-related increase in the systemic pro-inflammatory status. The process results in the breakdown of the multi-shell cytokine network as a consequence of remodeling of the innate and acquired immune system; leading to chronic inflammatory cyto kine production. Genetic, environmental and age-related factors determine susceptibility to inflammageing. Thus there is a diminished ability to modulate inflammation [Franceschi 2000].

These results imply that inflammageing is present in ageing tendons and aged individuals exhibit a reduced capacity to resolve inflammation. Therefore ageing may contribute to deregulated tendon repair through these pathways.

Reactive Oxygen Species and the Free Radical Theory

One ageing theory is the 'damage-accumulating theory/free radical theory' in which there is a progressive accumulation of cell damage resulting in failure of repair and maintenance systems [Harman 1956]. One of the causes of cell damage is reactive oxygen species (ROS). A free radicle is any species capable of independent existence that contains one or more unpaired electrons. Trauma, environmental and physiological stimuli may enhance ROS production and ROS are continually produced during normal cell metabolism.

There are a lack of studies on the role of ROS in age-related tendinopathy. An increase in the expression of peroxiredoxin, a thioredoxin peroxidase with antioxidant properties, in tendon degeneration suggests that oxidative stress may be involved in the pathogenesis of tendon degeneration [Wang 2001], as it is in the age-related disease osteoarthritis [Tiku 2000].

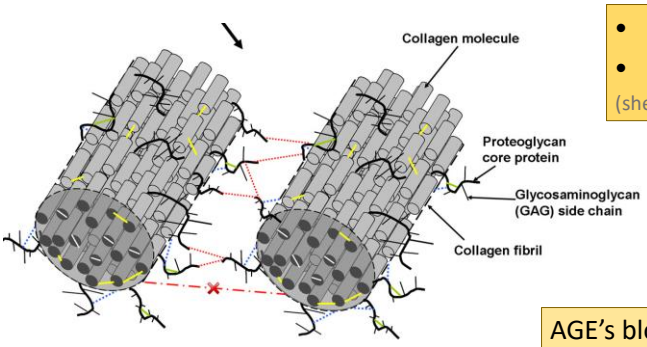
The long-lived nature of tendon collagen renders it susceptible to attack by reactive carbonyl groups on sugars such as glucose, in a process known as 'browning' or glycation. A series of spontaneous chemical re-arrangements occurs and further reactions with neighboring peptides results in advanced glycation end-product (AGE) crosslinks such as pentosidine.

For example pentosidine levels increase with age in human patellar tendon [Couppe 2009], posterior tibialis tendon [Corps 2012], and equine SDFT and CDET (Fig. 24.5) [Thorpe 2010]. The levels are however relatively low (1 crosslink per 70 collagen molecules) in the study by Thorpe et al. [Thorpe 2010] and other AGE crosslinks that are present at much higher levels are likely to be more relevant to pathophysiology. One AGE crosslink of particular interest is glucosepane; this AGE crosslink was first identified in 2002 by Biemel and colleagues [Biemel 2002]

with methylglyoxal resulted in increased stiffness of collagen fascicles and this

seemed to result from decreased sliding between collagen fibrils rather than increased stiffness of the fibril [88]. There remains much to be discovered about AGE formation as an ageing mechanism but this will undoubtedly be very important for understanding tendon homeostasis during ageing. Birch in Ackermann 2016 Ch 24>>

Cross-links



- Enzymatisch (LOX): Sterk
- AGE's: Stijf

(shear stiffness, bending stiffness)

AGE's blokkeren receptoren:
- Verstoorde schadeperceptie
- Verstoorde ontstekingsreactie
- Verstoorde MMP productie

21

<<The enzyme responsible for cross link formation lysyl oxidase (LOX) has been demonstrated to be necessary for optimal tendon fibrillogenesis since blocking of LOX does not influence the total amount of collagen synthesized, but markedly weakens the tendon structure and makes it more compliant (Herchenhan et al., 2015b). Magnusson 2018>>

<<It is now understood that the collagen fibril is a helically arranged supramolecular structure that can range in diameter from a few to several hundred nanometers, with lengths that may run on the order of centimeters [Craig 1989]. The mechanical competence of individual type-I collagen fibrils depends on the enzyme lysyl oxidase that regulates a robust formation of stable inter-molecular collagen cross-links during maturation [Bailey 2001]. The absence of these enzymatically mediated chemical bonds drastically diminishes collagen fibril strength and whole tissue function [haut 1985, Marturano 2014, Puxkandl 2002].

The essential functional role of enzymatic cross-linking in collagen fibril stability and whole tissue integrity has been convincingly demonstrated by accumulated experimental evidence [Haut 1985, Herschenhan 2015, Marturano 2014, Mosler 1985, Puxkandl 2002] and has been mechanistically supported by theoretical studies

as well [Kubo 2010]. At the core of mechanical cross-link function is the prevention molecular slippage, which in the absence of cross-links manifests as non-reversible fibrillar damage [Willet 2010]. Given that lysyl oxidase mediated collagen cross-links are so essential to the proper development of fibril structure and mechanical integrity, these are perhaps the best-characterized collagen crosslinkers.

Despite the fact that enzyme driven crosslinking plateaus after tissue maturity, connective tissue stiffness has been shown to further increase with age and diabetes [Bank 1998, Haut 1992, Lai-Fook 2000, Saito 2010, Sell 1992]. This non-enzymatically mediated tissue stiffening has been attributed in large part to oxidative reactions between glucose and collagen, and the related formation of so-called advanced glycation end-products widely known as AGEs [Avery 2005]. Due to the fact that AGE formation and accumulation are stochastic processes, it is more likely to occur in long-lived proteins [Avery 2006]. The low biological turnover of collagen thus makes it susceptible to interaction with metabolites such as glucose, and hyperglycemia related to diabetes is suspected to strongly predispose tissues of these patients to AGE accumulation (see Chap. 3) [Andreassen 1981, Snider 1982].

Very generally, the glycation reaction initiates with the formation of a reversible chemical bond, known as a Schiff base, between a carbohydrate, typically glucose, and a protein amino group (e.g., a collagen lysine side-chain) (Fig. 18.1). The unstable Schiff base may eventually reverse or can become a stable intermediate structure commonly referred to as an Amadori product. Afterwards, a complex series of reactions that take place over the course of months or years lead to various metabolic byproducts of glycolysis including the products glyoxal, methylglyoxal and 3-deoxyglucosone, all of which can interact with extracellular proteins to form AGEs [Ahmed 2005]. Some AGEs can bridge between the free amino groups of neighboring proteins to form inter-molecular cross-links, while others known as 'adducts' affect only a single molecule [Grandhee 1991]. Among the different AGEs, the most abundant known AGE cross-link in collagen tissues is glucosepane, a lysine-arginine cross-link [Monnier 2005, Sell 2005].
The potentially causative relationship between AGE cross-linking, altered tissue properties, and subsequent tissue pathology has long been posited, and in fact seems plausible on the basis of the well documented correlation between AGE markers (pentosidine; auto-fluorescence) and increasing tissue stiffness [Bailey 1998, de Jonge 2015].

Our own experimental efforts using tissue explants under carefully controlled conditions of accelerated AGE formation have provided support to previous less direct evidence that collagen fibril stiffness remains unaffected by effects of AGEs, discounting the thesis that increased fibrillar stiffness underlies the tissue level changes reported in diabetic tendon [Fessel 2014].

We have documented, however, that drastic changes in tissue viscoelasticity occur with intensive tissue glycation — particularly the effective elimination of lateral sliding between adjacent collagen fibers within a tendon fascicle [Li 2013]. Thus what is often perceived as "tissue stiffening" rather likely reflects loss of tissue gliding mechanisms — the clinically observable effect of which may more precisely be described as "shear stiffening" or "increase bending stiffness" (please also see Chap. 19) (Fig. 18.2).

Most potentially important cellular consequences of collagen glycation relate to modified collagen-protein and collagen-receptor interactions [Avery 2006]. Here the formation of AGEs adducts or cross-links) on specific amino acids involved in intermolecular recognition and binding could lead to dramatically modified interactions between collagen and other molecules. These consequences may involve tendon proteoglycans and bound growth factors, matrix binding cell receptors such as integrins, or the activity of cell secreted enzymes — with all these factors potentially contributing to inhibited wound repair and an aberrant inflammatory response [Bedi 2010, Frank 1995].
Altered kinetics of the matrix degrading enzyme family matrix metalloproteinases (MMPs) come under particular scrutiny, as AGE cross-links have been demonstrated in vitro to reduce sensitivity to collagenase (see Chap. 17) [Reddy 2004, Reddy 2002].

Although mechanical forces and resulting matrix deformations lie at the center of tendon homeostasis, the mechanisms by which extracellular mechanics regulate tissue maintenance and repair are only beginning to be understood.

Mechanical testing of rat tail tendon with induced AGE cross-links showed nearly complete removal of the lateral fiber— fiber movements inside the fascicle that dominate normal tissue response to mechanical tension, while AGE laden tendons demonstrate a pronounced shift to fiber stretching relative to fiber sliding. While it remains to be investigated, such changes in cell-level stimuli can plausibly be expected to adversely affect the ability of tendon cells to detect local changes in mechanical tissue loads, such as those related to mechanical matrix damage. If such mechanical feedback loops are altered, the ability of tendon cells to maintain tissue in a functional, healthy state may also be impaired. Snedeker in Ackermann 2016 Ch 18>>

<<The stiffness of the inter-fascicular matrix however, which binds the fascicles together, increased in stiffness significantly with increasing age (Fig. 24.3) [Thorpe 2013] This finding suggests that the load distribution within the tendon changes with ageing such that the fascicles are loaded earlier during tendon extension in older tendons. It is interesting to note that behavior of the subunits of tendon differ between tendon types; in the equine common digital extensor tendon (CDET), a

positional tendon, the interfascicular matrix is much stiffer [Thorpe 2012] and does not change significantly with increasing horse age (Fig. 24.3) [Thorpe 2013]. Birch in Ackermann 2016 Ch 25>>

Obesitas

Buikvet belangrijker dan BMI
(bij mannen)

Peesbelasting door gewicht
Laaggradige ontsteking
Peptiden uit adipocyten
Hoge glucose spiegel → AGE's

22

<< Several epidemiological and clinical observations have definitely demonstrated that obesity has harmful effects on tendons. The pathogenesis of tendon damage is multi-factorial. In addition to overload, attributable to the increased body weight, which significantly affects load-bearing tendons, systemic factors play a relevant role. Several bioactive peptides (chemerin, leptin, adiponectin and others) are released by adipocytes, and influence tendon structure by means of negative activities on mesenchymal cells. The ensuing systemic state of chronic, sub-clinic, low-grade inflammation can damage tendon structure. Metabolic disorders (diabetes, impaired glucose tolerance, and dislipidemia), frequently associated with visceral adiposity, are concurrent pathogenetic factors. Indeed, high glucose levels increase the formation of Advanced Glycation End-products, which in turn form stable covalent cross-links within collagen fibers, modifying their structure and functionality.

Sport activities, so useful for preventing important cardiovascular complications, may be detrimental for tendons if they are submitted to intense acute or chronic overload. Therefore, two caution rules are mandatory: first, to engage in personalized soft training program, and secondly to follow regular check-up for tendon pathology.

Plantar fasciitis is very common in overweight and obese subjects, due to the

increased stress on foot structures [Frey 2007, Irving 2007]. Riddle et al. [Riddle 2003], in a study enrolling 50 subjects with plantar fasciitis and 100 controls, observed that participants with a BMI >25 were 5.6 times more likely to be affected when compared with subjects with BMI <25.

Similarly, patients with Achilles pathology exhibited significantly higher BMI than controls, even after accounting for age. In panicular, overweight and obese were 2,6 to 6,6 times respectively more likely than patients with normal BMI to be affected by Achilles tendinopathy ($p < 0,001$) [Scott 2013]. Further studies have shown that in men waist circumference is a better predictor of tendon pathology than BMI [Gaida 2009, Holmes 2006, Klein 2013]. Indeed, asymptomatic Achilles tendon pathology was found associated with central fat distribution in men (i.e. an increased waist/ hip ratio, WHR), whereas it was associated with peripheral fat distribution in women. Considering surgery, overweight patients with recalcitrant Achilles tendinopathy experience more prolonged recovery times, more post-intervention complications, and a greater risk of further procedure than normal weight subjects [Maffulli 2006] (Fig. 15.1).

The results showed that MRI features of patellar tendinopathy were common in the general population (28 %), and that current weight (p 0,002), BMI ($p = 0,002$), heaviest lifetime weight ($p = 0,007$) and weight at age of 18—21 years (p 0,05) were all positively associated with the prevalence of the tendinopathy [Fairley 2014] (Fig. 15.2).

In conclusion, the majority of studies suggest that overweight and obesity are significantly associated to symptomatic tendinopathies or to abnormal tendon structural features, which in turn are important predictors of a future clinically evident pathology. The association, in general, is more evident for lower-limb than for upper-limb tendons. However, most of published studies are observational, and therefore do not allow a precise identification of a cause-effect relationship between adiposity and each type of tendinopathy. Therefore, further research is necessary to better clarify the role of adiposity "in se", excluding the pathogenetic relevance of associated factors, such as aging, the level of overuse and metabolic disorders.

The increased body weight has also significant impact on tendons. It is well known that mechanical loading is essential to maintain tendon homeostasis, but, when the loading magnitude is abnormal, as can happen in obese subjects, the tendon response reverses from beneficial towards degenerative.

Briefly, there is an exceeding production of proteoglycans and inflammatory molecules, with increased metalloproteinase expression, which leads to the formation of degradation products and water retention. This failed healing process

favors a smoldering fibrogenesis, with matrix turnover without normal maturation [Abate 2013, Battery 2011]. This information comes mainly from studies performed on Achilles tendon in runners. Indeed, during running, the tendon is highly solicited and the load can be as high as eight times body weight, so that modest increases in weight are amplified within the tendon [Abate 2012 nantel 2011]. Broadly speaking, these concepts can be applied to all tendons, which are selectively stressed in various athletic activities: the shoulder in swimming and basket, the elbow in tennis and golf, and the knee and ankle in all sports characterized by running and jumping.

Systemic Hypothesis

Adipose tissue can be considered as a major endocrine and signaling organ [Abate 2013, Rechahardt 2014]. Several bioactive peptides and hormones are released by adipocytes, among them a full range of proteins (chemerin, lipocalin 2, serum amyloid A3, leptin and adiponectin), which can influence tendon structures by means of various activities on mesenchymal cells. In particular, inflammatory mediators (cytokines, prostanoids, and metalloproteinases) can be modulated [Gaida 2009], and the subsequent systemic state of chronic, sub-clinic, low-grade inflammation (increased serum levels of PGE2, TNF-a, and LTB4) can damage tendon structure. The cumulative harmful effect of these substances may explain tendon damage both in load-bearing and non loadbearing tendons of obese subjects.

Tendon damage can be amplified by a cluster of metabolic disorders frequently associated with obesity [Abate 2015]. As shown by epidemiologic studies, obese subjects with visceral fat deposition are more predisposed to tendinopathies. Interestingly, this relationship has been also observed in individuals with an increased fat mass and higher WHR, despite having a normal BMI. These subjects, classified as metabolically obese but normal weight, account from 5 to 45 % of the general population [Conus 2007]. Therefore, it may be hypothesized that tendon pathology is strongly linked to metabolic syndrome, characterized by insulin resistance, diabetes, or impaired glucose tolerance, hypercholesterolemia, hypertriglyceridemia, and low levels of HDL cholesterol. In the presence of increased glucose levels, the formation of Advanced Glycation End-products (AGEs) is markedly accelerated (see Chap. 14, 16, 17, 18, and 19). [Abate 2011, Del Buono 2011, Gauterie 2014]. A key characteristic of reactive AGEs is the formation of stable covalent cross-links within collagen fibers, which alter their structure and functionality. Moreover, AGEs react with a variety of AGE-binding receptors on the cell surface, which in turn activates several critical molecular pathways and triggers a number of effects. These include pro-oxidant events via generation of reactive oxygen species and led to a sustained up-regulation of pro-inflammatory mediators [Matsuura 2005].

Actually, this is an important issue, because what is beneficial for improving metabolism and preventing important systemic diseases may be detrimental for

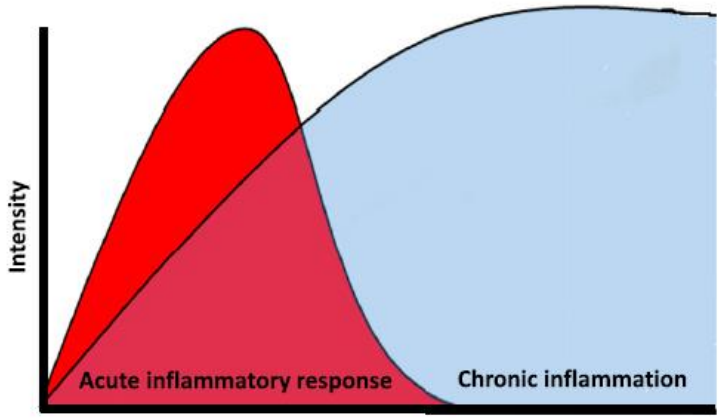
tendons, which are submitted to acute or chronic overload. Indeed, the risk of developing a symptomatic tendinopathy, and even of undergoing a tendon rupture, is substantially increased in obese subjects, whose tendons are frequently weakened by a sub-clinical damage and by a metabolically disturbed milieu [Abate 2012]. Therefore, minimizing the impact of tendon pathologies when prescribing exercise and sport activities as medicine for weight reduction in sedentary individuals becomes mandatory. In real life, several persons practice running, for several reasons: it is inexpensive, may be practiced by oneself every time he/she wants, and may be performed by people lacking of any skill in specific sports activities. However, running is deleterious for load-bearing tendons, and Achilles tendon in particular, which is highly solicited. Otherwise, tennis, soccer, basketball, and other contact sports can expose tendons to sudden intense, even short-lasting, stress, avoring microruptures of collagen fibers.

More importantly, it is very difficult to disentangle the role of metabolic disorders obesity-related, such as impaired glucose tolerance and hyperlipidemia. Actually, more than by the increased BMI, a major role seems to be played by visceral fat deposition, which is associated with the metabolic syndrome and a chronic state of low-grade inflammation. Experimental and clinical research has highlighted several pathogenic mechanisms, which can be responsible of tendon damage. In particular, it has been shown that the biochemical milieu, around tenocytes and other tendon cells and structures, largely influences the tendon response to mechanical loading, reversing it from beneficial to degenerative. Abate in Ackermann 2016 Ch Ch 15>>

<<In line, men with Achilles tendinopathy are older and have a high waist circumference [Gaida 2010]. Elevated adiposity is frequently associated with tendon pathology [Gaida 2009] in a review with a total number of 19.949 individuals. In 43 % of cases, the group with tendinopathy had significantly greater adiposity levels than the control group without tendinopathy. Two other key findings of that review are worth repeating. First, when upper-limb and lower-limb tendinopathies were compared the association with adiposity was equally strong. As the lower-limb tendons support body-weight while the upper-limb tendons support only the weight of the limb, this finding suggested that mechanical loading does not fully explain the association between adiposity and tendinopathy. Second, the longitudinal studies in the review that showed baseline adiposity predicted tendinopathy at follow-up suggested that adiposity is a risk factor for tendinopathy rather than a consequence of tendinopathy. Knoblauch in Ackermann 2016 Ch 22>>

Ontsteking

'Inflammation triggers degeneration'



23

<<Whilst an acute controlled inflammatory response to injury can be adaptive and protective, it can be detrimental if unregulated and chronic. Furthermore, inflammation can also occur when the normal homeostasis of physiological systems are disrupted, for example by stresses, hypoxia and metabolic diseases (see Chaps. 9—18), and in this context may represent a pathological rather than protective process [Medzhitof 2008].

Cellular and Molecular Mediators of Inflammation
A helpful review of the origin and physiological roles of inflammation is provided by Medzhitof [Medzhitof 2008], who describes exogenous initiators of inflammation as those that are either microbial, or non-microbial including foreign bodies, toxins, allergens and irritants. Endogenous inducers are less well defined and understood, but include signals from stressed or damaged cells (for example due to disease), products of ECM breakdown, crystals such as urate and calcium pyrophosphate (see Chaps. 10, I l and 12), lipopolysaccharides, collagen etc

Most of our understanding of inflammatory pathways relates to the exogenous agents or macrotrauma. It is not known how closely these processes apply in the context of low-grade chronic mechanical tissue microtrauma, and in endogenous

tissue stresses such as metabolic diseases and systemic inflammation. Once initiated, the typical acute inflammatory response has the purpose of adaptation to the insult and returning the tissue to its normal baseline homeostatic state. If the inflammatory stimulus persists then a maladaptive state of chronic inflammation arises.

In obesity, hypertrophic adipocytes secrete chemoattractants that draw immune cells into the tissue (see Chap. 15). Other endogenous initiators of inflammation include advanced glycation end products (AGEs) (see Chap. 18) and oxidized lipoproteins (such as high-density lipoproteins and low-density lipoproteins) [Brownlee 1988].

Evidence for Inflammation Across the Spectrum of Tendon Disease
Inflammation plays a variable role in tendon disorders, and is influenced not only by mechanical stresses but also by underlying disease processes such as metabolic, endocrine, and autoimmune diseases, drugs, and patient characteristics (age, genetics, other comorbidities, eg. gender). It appears that all forms of the tendon can be affected, including the core tendon, tendon sheath and enthesis

Studies of humans with tendinosis have failed to show significant inflammatory cells around lesions [Puddu 1976, Riley 2008] leading to the dogma that inflammation plays little or no role in tendinosis [Khan 2002]. Developments in immunohistochemistry and molecular biology have led to this belief to be challenged [Rees 2014]. Clearly there is much more work to be done in this field but it is worth emphasising the rationale for considering inflammatory mechanisms in tendon disease.

T and B lymphocytes have been identified in chronic Achilles tendinopathy [Schulze-Tanzil 2011]. Increased levels of proinflammatory mediators including IL-I, IL-6, Cox-2 and Substance P have been found [Fenwick 2000, Gotoh 1997, Gotoh 1998, Legerlotz 2012, Sullo 2001, Zhang 2010]. Prolonged exercise is associated with increased peritenidous levels of PGE2, thromboxane, bradykinin and IL-6 in peritendinous tissue [Langberg 2002, 1999]. All are proinflammatory. Furthermore, increased levels of cyclooxygenase-2 (COX-2) are seen in patellar tendinosis [Fu 2002], and repeated injection of PGE2 around tendon causes degenerative changes. These findings are not entirely straightforward, since PGE2 may also have antiinflammatory effects [Riciotti 2011]. Furthermore, Clearly there are other reasons for pain in tendinosis, since PGE2 levels are not correlated with pain.
Once initiated, by whatever trigger, tendinosis involves collagen disruption and degradation, extracellular matrix changes and tenocyte apoptosis [Riley 2008]. Inflammation may act as an initial trigger to these 'degradative' processes seen in human tendons and may still play a role in the progression of tendon disease.

These proinflammatory cytokines are produced both by leucocytes and tenocytes in

response to trauma and exercise (which can have effects not only through loading but also hypoxia). They affect extracellular matrix (ECM) homeostasis, accelerate remodeling, amplify biomechanical adaptiveness and promote tenocyte apoptosis. There are multiple interrelations between cytokines and tendon ECM synthesis, catabolic mediators such as matrix-degrading enzymes, inflammatory and angiogenic factors (COX-2, PGE2, VEGF, NO) and cytoskeleton assembly [Schulze-Tanzil 2011].

Tendinosis.
Its pathophysiology is still not clear. It may be driven by hypoxia, which is common in metabolic diseases and in exercise. VEGF, produced by macrophages is considered to play a role. It has a proinflammatory action but also has other mechanisms by which tendons can be damaged, including upregulation of MMPs, and down regulation of TIMP [Magnan 2014]. The presence of neural sprouting with angiogenesis is relevant to considering the role of inflammation. 'Neurogenic inflammation' the release of pro-inflammatory mediators such as Substance P, Calcitonin gene related peptide and calcitonin and endothelin — may contribute to the progression and the pain of tendinopathy [Magnan 2014].

Hypoxia promotes the expression of proinflammatory cytokines, key apoptotic mediators and drives matrix component synthesis towards a collagen type Ill profile by human tenocytes. [Millar 2012].
Tendon abnormalities, both of load bearing and non-load bearing tendons, are more common in individuals with higher adiposity. This is particularly the case for males and oestrogen may provide a protective benefit. Adiposity has an effect even if the subject is of normal weight [Abate 2014, gaida 2010, Gaida 2009, Warrander 2011, Wendelboe 2004], emphasising that although increased mechanical stresses and the effects of consequential fibre disruption undoubtedly drives some of the tendon changes seen in obese subjects, the systemic effects of adiposity play a significant role. Proinflammatory mediators including TNF-u, PGE2 PGE2, and LTB4 are seen in obesity.

Insulin resistance is often associated with obesity and other metabolic and systemic diseases, and it plays a potentially pivotal role in the development of tendinopathies. When blood glucose availability is increased, the production of AGE's (proinflammatory initiators, discussed earlier) is markedly elevated. These are not only associated with protein degradation, but also with nitric oxide destruction and growth factor inhibition, increasing apopotosis through oxidative stress and increased activity of pro-apoptotic and proinflammatory cytokines.

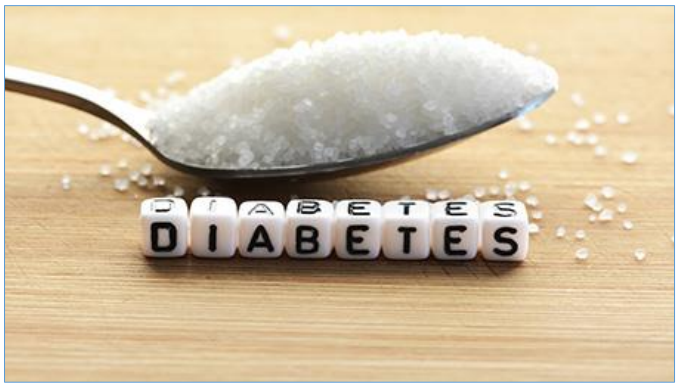
Studies on the histopathology of the acute phase of tenosynovitis are scant. However the synovium rather than the tendon proper may be the primary initiating site of inflammation, which would explain why primary disorders of synovium such as

rheumatoid arthritis frequently involve the tenosynovium and present as tenosynovitis. Speed in Ackermann 2016 Ch 20>>

<< Adipose Tissue and Tendons
Fat pads, such as the Kager's fat pad [Ly 2004] of the foot or the Hoffa fat pad of the knee do play a role in inflammation in tendinopathies of the associated tendons, the insertional Achilles tendon for the Kager's fat pad and the Hoffa fat pad for the patella tendon. As such, patients suffering from Achilles tendinopathy especially in insertional cases demonstrate an increased soft tissue density of the Kager's fat pad in association with an increased Achilles tendon diameter [Pingel 2015].

The infrapatellar fat pad (Hoffa's fat pad) may degenerate to a chronic edema with subsequent soft tissue impingement, ischemia and lipomatous tissue necrosis [Hoffa 1904, Magi 1991]. The Hoffa fat pad may contain a number of inflammatory cells as well as is a source of adipokines, cytokines and grows factors modifying disease [27]. Adiponectin has been shown to induce matrix metallaproteinase-l and interleukin-(IL)6 expression in synovial fibroblasts and thus, may exert inflammatory functions [Tang 2007, Gomez 2009]. Knoblauch in Ackermann 2016 Ch 22>>

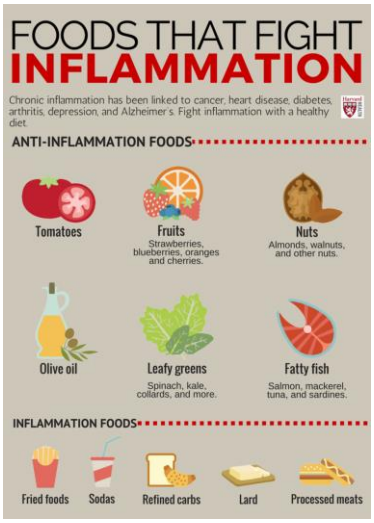
Diabetes



24

<<Observations in Diabetes Mellitus
It has recently been demonstrated that patients with metabolic disorders such as diabetes mellitus are at greater risk of developing various musculoskeletal disorders [Pradhan 2009]. Thus, diabetics often exhibit neuropathy and also decreased levels of sensory neuropeptides, which may be associated with defective tissue healing [Pradhan 2009]. Diabetes is associated with impaired connective tissue healing and reduced biomechanical properties, correlated to down-regulated extracellular matrix proteins [Ahmed 2012].
Ackermann in Ackermann 2016 Ch 4>>

Voeding



25

<<There is very little direct research to conclusively prove the relevance of diet in primary tendinopathies, however it seems prudent to ask whether our current knowledge about the impact of nutrition on collagen metabolism could be useful in assessing, preventing, or treating tendinopathy.

One could hypothesize that a tendinopathy might develop in part through dietary impairment of tenocyte metabolism leading to reduced structure/function of the load-bearing tissue. Alternatively, a diet which either helps or hinders tendon healing (e.g. by influencing inflammation-repair responses) could influence the development and the prognosis of tendinopathy.

This appears to be an area ripe for future research. Additionally, whereas type I collagen is relatively long-lived in the extracellular matrix, glycosaminoglycans -- important for tendon hydration, regulation of collagen fibril assembly, and inter-fascicular gliding —are shorter-lived and could therefore be influenced quite rapidly by changes in diet.

Nutrition and Tendons
Having a basic knowledge of nutrition is important for clinicians, because nutrition is

vital for growth and development, and for the prevention and treatment of disease [Ohlhorst 2013]. Nutrients fall into three main categories macronutrients, micronutrients and water [Molnar 2014]. Macronutrients, consisting of carbohydrates, proteins and lipids, are dietary substances which the body requires in large and regular quantities [Molnar 2015]. Carbohydrates are a major source of energy, of which the largest part is used to fuel muscle and brain tissue [Clark 1997]. Protein is essential for building and repairing muscles, red blood cells and other tissues as well as for synthesizing hormones [Clark 1997]. Dietary protein is broken down into amino acids, which are then utilized according to specific requirements [Clark 1997]. Lipids are a rich source of stored energy [Clark 1997]. Vitamins and minerals are considered micronutrients, and they are required in lesser amounts [Molnar 2014]. Vitamins act as metabolic catalysts that regulate chemical reactions in the body — e.g. see discussion of Vitamin C below [Clark 1997]. Minerals are used to form structures of the body as well as help regulate body processes — e.g. matrix metallo-proteinases are zincdependent enzymes which play key roles in tendon metabolism and healing [Clark 1997]. Many micronutrients, known as essential nutrients, cannot be made by the body therefore they need to be ingested through food or dietary supplementation.

Considering the many steps — both enzymatic and non-enzymatic — that are involved in collagen synthesis, errors or deficiencies can occur at multiple points throughout the process, and these could ultimately affect the quality and tensile strength of the resulting collagen molecules. The remaining paragraphs discuss how certain nutritional factors could influence the synthesis of collagen in tendons.

Vitamins

Vitamins act as catalysts of biochemical reactions [Clark 1997]. Most vitamins are not produced by the human body, therefore they need to be ingested. Current research suggests that vitamins C and D may influence the metabolism and/or structure of tendons.

Vitamin C

Deficiency of vitamin C (ascorbic acid) is not common in the general population of developed countries, but it does present in individuals with poor nutrition or impaired digestion, e.g. patients who are alcoholic, critically ill, undergoing chemotherapy, etc.

Vitamin C is a potent inducer of collagen synthesis in tendon cells [Kipp 1990]. Following tendon injury, when collagen synthesis is maximal, vitamin C requirements to achieve optimal healing may be higher than the levels typically experienced by tenocytes [Russell 1991]. Repeated injections of 150 mg of Vitamin C to injured rat tendons resulted in accelerated healing compared to controls [Omeroglu 2009].

Vitamin D

Vitamin D is also known to have a direct impact on collagen synthesis by tendon fibroblasts. The addition of Vitamin D3 and D2 metabolites to human-derived tendon fibroblasts revealed a dose-responsive, anabolic effect, with progressive increases in mRNA levels of type I collagen [Poulsen 2013]. In these same experiments, vitamin D also reduced the levels of intracellular reactive oxygen species. These findings led the authors to suggest that vitamin D has a beneficial effect on tendon, and that vitamin D deficiency may have a negative effect on tendons by limiting type I collagen synthesis and increasing their exposure to reactive oxygen species.

This anti-inflammatory effect has also been observed in ligament fibroblasts [Hosokawa 2015]. In ligament fibroblasts, vitamin D also inhibited osteoblastic differentiation and calcification [Chen 2012].

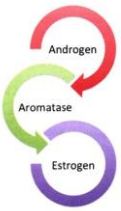
Overall, the impact of vitamin D on collagenrich tissues such as tendon could be potentially beneficial, particularly after injury, but clinical studies are lacking.
Within each dietary grouping, some rats were allowed to exercise and the remainder were sedentary [Barbosa 2012]. The main finding of this study was that the leucinerich diet stimulated collagen synthesis in the tendon more than a standard diet, especially when combined with exercise [Barbosa 2012]. Leucine increased the amount of hydroxyproline [Barbosa 2012], which is a major component of collagen, and it also plays a key role in the stability of the collagen fibres. The amino acid glycine has been demonstrated to have a direct effect on an inflamed Achilles tendon in rats. One study found that a diet containing 5 % glycine induced the synthesis of hydroxyproline and glycosaminoglycans, allowing for a faster restructuring of the collagen molecules [Vieira 2015]. This resulted in the tendon being more resistant to rupture, offering preliminary support for the hypothesis that dietary supplementation with glycine could be effective for individuals with injury of the Achilles tendon [Vieira 2015].

Many environmental factors (UV light, pollution, cigarette smoke) are known to also cause increased ROS. Natural sources of antioxidants are available in fruits (grapes, berries), vegetables (dark greens), spices (ginger, curcumin), grains (whole grains), herbs (rosemary, oregano), and tea (green tea) [Lü 2010].

Although limited, there is evidence to suggest that high concentrations of free-radical oxidants may be involved in tendon pathology [30]. One trial investigated the efficacy of polyunsaturated fatty acids and antioxidants on tendinopathies, with the findings supporting the use of dietary supplementation in its management [Lewis 2009]. Scott in Ackermann 2016 Ch 27>>

Medicijnen

1. Corticosteroiden
2. Chinolon antibiotica
3. Aromatase inhibitors
4. Statins



26

<< Drug-induced tendon disorders are an often underestimated risk factor. The range from detrimental effects on the tendon include tendinopathy as well as potentially tendon rupture. As for today, four main drug classes have been reported to be associated with potentially deteriorated tendon properties

1. Corticosteroids, 2. Chinolon antibiotics 3. Aromatase inhbitors, 4. Statins as HMG-CoA-reductase inhibitors. Most often, the Achilles tendon is affected in terms of tendinopathy and/or subsequent tendon rupture. However, nearly every tendon of the entire body might be affected in a detrimental way by one or a combination of the aformentioned agents.

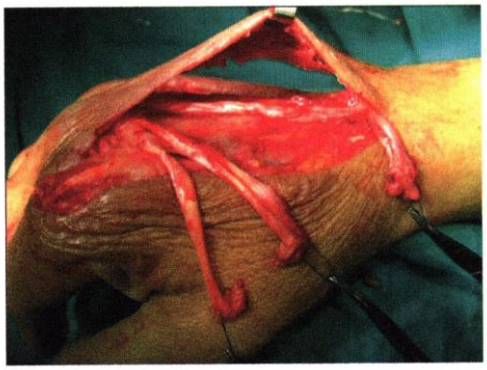
<u>Chinolone Antibiotics</u>
Chinolone antibiotics are broad spectrum antibacterial drugs against both, gram-negative and gram-positive bacteria. The majority of chinolones are fluorochinolones. In bacteria, fluorochinolones inhibt selectively the topoisomerase II ligase domain leading to DNA fragmentation.
Hyaline degeneration and fibre disarrangement were observed in the tendons of the ciprofloxacin, pefloxacin, and ofloxacin treated-groups, whereas myxomatous degeneration was observed only in the ciprofloxacin and pefloxacin groups.

Aromatase Inhibitors

Aromatase inhibitors are used to decrease circulating estrogen levels in postmenopausal women. Aromatase is the responsible enyzme for the conversion of androgens in estrogens (Fig. 22.9). As such, aromatase inhibitors block this conversion (Fig. 22.10). This principle is increasingly used as an adjuvant therapy in postmenopausal women with hormone receptorpositive invasive breast cancer [Goss 2005, Winer 2005].

Musculoskleletal adverse effects typically arise within 3 months of therapy initiation [Henry 2008]. A MRI study revealed a significant number of wrist problems with tenosynovitis among these females [Morales 2006] (Table 22.2). Knoblauch in Ackermann 2016 Ch 22>>

Corticosteroïden



(Knoblauch 2016)

Pees ruptuur na 2 injecties in de pols

27

<<Repeated corticosteroid injections appear to increase the risk of a tendon rupture.

Beyond the antiinflammatory effect of corticosteroids, tendons might substantially suffer in the following. Clinically, tendon rupture typically occur some 2—6 weeks following a corticosteroid injection, such as at the Achilles tendon level [Kearney 2015].

The largest clinical metaanalysis, published 2010 in the Lancet by Coombes and coworkers [Coombes 2010] with 41 included randomized trials and 2672 participants showed that corticosteroid injections reduced pain in the short term compared with other interventions, but this effect was reversed at intermediate and long terms. Knoblauch in Ackermann 2016 Ch 22>>

<<Glucocorticoids are generally used to relieve pain and/or inflammation in a wide variety of musculoskeletal disorders including osteoarthritis, inflammatory arthritis, tendinopathy and degenerative spine disease. Glucocorticoids reduce tendon derived cell proliferation in vitro and reduce extracellular matrix synthesis both in vitro and in vivo, in particular type I collagen synthesis. Glucocorticoids also appear to result in acute deleterious changes in healthy in vivo tendon including collagen necrosis,

collagen disorganisation and inflammatory cell infiltration; while the overall effect of glucocorticoid administration on the mechanical properties of healthy in vivo tendon are generally negative. Overall the existing in vitro and in vivo evidence suggests that glucocorticoids should be used with caution in treating painful tendinopathy. Certainly a real need exists to follow up the long term clinical effects of glucocorticoid in treating tendinopathy, as there is currently a paucity of evidence in this area. However in this context while the short term benefits are clear, glucocorticoids remain a useful treatment option provided they are used in the right patients in sensible moderation.

The In Vitro Effects of Glucocorticoid

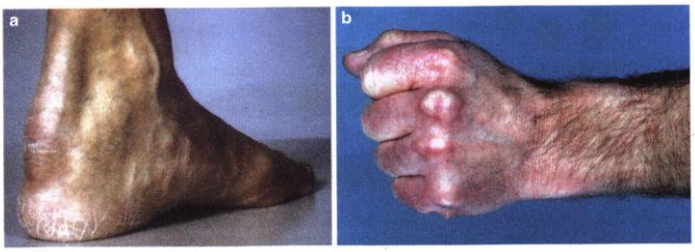
Broadly it has been repeatedly demonstrated that glucocorticoids reduce both cell proliferation and collagen synthesis in vitro (Fig. 23.1) [Dean 2014]. Poulsen et al. [Poulsen 2011] demonstrated that dexamethasone reduced tendon derived cell proliferation, as well as reduced collagen and glycosaminoglycan synthesis, and that reactive oxygen species (ROS) were increased.

The In Vivo Effects of Glucocorticoid

Difficulties in carrying out human in vivo studies mean that the majority of in vivo work has been carried out in animals. There is certainly some evidence that glucocorticoids have significant deleterious effects on tendon in vivo in terms of inducing collagen bundle fragmentation and an influx of inflammatory cells [Akpinar 2002, Tillander 1999, Muto 2014]. A notable point is that these deleterious effects were only seen after relatively high doses of glucocorticoid which were repeated multiple times within a relatively short space of time, and that deleterious effects were not seen with less frequent injections [Tillander 1999].

Broadly the effects of glucocorticoid on the mechanical properties of tendon appear to be negative [Dean 2014]. Figure 23.2 shows a forest plot demonstrating the overall negative effect of glucocorticoid on the mechanical strength of tendon. This finding is consistent the evidence that demonstrates glucocorticoid administration results in collagen necrosis and disorganisation, followed by an infiltration of inflammatory cells. Dean in Ackermann 2016 Ch 23>>

Statines / hypercholosterolemie



Xanthoma's

(Soslowski 2016)

28

<< Statins

Statins are a cholerestrol-lowering drugs blocking the HMG-CoA-Reductase. In cardiovascular disease such as coronary artery disease, statins have been proofed to be beneficial. More recently, additional positive clinical results have been published such as in new onset atrial fibrillation [33]. Statins are believed to remodel the cytoskeletal architecture and mediate various anti-inflammatory, antioxidant, and antiproliferative effects that might limit endothelial dysfunction [Bhandari 2015].

Experimental studies in rats revelaed that simvastatin, atorvastatin and rosuvastatin caused a deterioration of the biomechanical properties of the Achilles tendon (see Chap. 14) [Kaleagasioglu 2015].

Notably, on the other hand, simvastatin as a statin has been reported recently to reduce fibrosis and protects against muscle weakness in a experimental model in rats with a full-thickness supraspinatus tear [Davis 2015]. In line, similar beneficial effects of atrovastatin have been underscored by Dolkart et al. in an experimental rat rotator cuff model [Dolkart 2014]. The results indicate that atrovastatin enhances tendon healing by stimulating tenocyte proliferation, migration, and adhesion via increased COX2 activity and autocrine/paracrine PGE2 signaling. These findings also

demonstrate that this effect is mediated by EP4 signaling.
Therefore, the amount and the timing of statin therapy may well play a role whether any detrimental or potentially benefical effects of statins on tendon properties is observed. While direct detrimental effects of statins on tendons have been shown as aforementioned, the experimental data on rotator cuff healing might warrant further investigations. Knoblauch in Ackermann 2016 Ch 22>>

<<Hypercholesterolemia is a serious health problem that is associated not only with heart disease, but also tendon pathology. In high cholesterol environments (e.g. familial hyperlipidemia), lipids accumulate within the tendon extracellular matrix and form deposits called xanthomas. Lipidrelated changes are known to affect several tendon mechanical properties, including stiffness and modulus, in uninjured and injured tendons, alike. Mechanisms to explain these cholesterol related changes are multiple, including alterations in tenocyte gene and protein expression, matrix turnover, tissue vascularity, and cytokine production. Clinically, rotator cuff tear and Achilles tendon rupture are clearly associated with metabolic derangements, and elevated total cholesterol is often among the specific metabolic parameters implicated. Treatment of hypercholesterolemia using statin medications has also been shown to affect tendon properties, resulting in normalization of tendon thickness and improved tendon healing. Despite current work, the pathophysiology of lipid-related tendon pathology remains incompletely understood, and additional hypothesisgeneratin studies, including those incorporating whole-genome and whole-transcriptome technologies, will help to point the field in new directions.

Hypercholesterolemia is associated with heart disease [2, 3] and is why cholesterol-lowering drugs are some of the most widely prescribed medications in our healthcare system. Hypercholesterolemia is also associated with tendon pathology, and, in patients genetically predisposed to hypercholesterolemia, there are increased rates of tendon rupture [2—4] (see Chap. 10).

For example, in one case series of 41 patients who underwent surgical treatment for Achilles tendon rupture, serum total cholesterol was elevated in 83 %, but only 19 % of patients were aware of their condition [6].

How Lipids Accumulate Within Tendons; Formation of Tendon Xanthoma
High serum cholesterol (also referred to as "lipid") levels allow for the accumulation of oxidized low-density lipoproteins (LDL), which are cholesterol carrier proteins that include modified phospholipids and cholesterols, isoprostanes, oxidized arachidonoyl residues, lysolipids, and lysophosphatidic acid [7]. Many of these oxidized lipids possess platelet stimulatory properties, which in the context of heart disease contribute to arterial thrombus formation after rupture of atherosclerotic plaques. In addition to platelet acti vation, LDL also produces a more general local inflammatory

response and contributes to cell death through activation of the intrinsic apoptotic signaling pathway within mitochondria [8].
The clinical manifestation of lipid accumulation in human tendons is a tendon xanthoma and represents the major tendon pathology observed in patients with familial dyslipidemias. Xanthomas are collections of lipid-laden macrophages around tendon. By dry weight, xanthomas are composed of 33 % lipids and 24 % collagen [9]. The lipid component is made up of 55 % free cholesterol, 28 % cholesterolesters, and 13 % phospholipids [10].

Unlike xanthomas in type Il disease, xanthomas in type Ill disease are typically asymptomatic.

Tendon involvement can be unilateral or bilateral, and patients who are symptomatic may report up to 12 attacks of pain per year [4]. In one study of 73 patients with heterozygous type Il hyperlipidemia, 18 % of patients reported Achilles pain, and in 11 % of patients there was evidence of tendonitis [14]. A subsequent cross-sectional study reported that 46.6 % of patients with familial heterozygous type Il hyperlipidemia had one or more episodes of Achilles pain lasting longer than 3 days, as compared to 6.9 % of unaffected controls [23].
Together, these data suggest that elevated cholesterol levels may alter the tendon microenvironment via local changes in protein synthesis and extracellular matrix composition/turnover.

Statin Therapy is Associated with Tendon-Related Side Effects in Patients with Hypercholesterolemia
The pharmacological treatment of hypercholesterolemia — using statins, bile acid sequestrants, ezetimibe, and niacin — has been associated with regression of tendon xanthomas [45—47].

Despite allowing for normalization of tendon thickness in at least a subset of patients, the use of lipid-lowering medication to treat hyperlipid emia may also result in at least transient changes that are detrimental to tendon structure and func tion. Of all lipid-lowering medications, statins are the most commonly prescribed. Tendon injury accounts for 2.1 % of reported statinrelated side effects. 59 % of these cases occur within the first year of therapy, and median time from statin initiation to tendon injury is 8—10 months [49]. Among patients who report tendon-related side effects, approximately two-thirds of patients experience tendinopathy alone, while the remaining one-third experience frank tendon rupture. The Achilles tendon is most commonly affected (52 % of cases) [50]; other areas of involvement include rotator cuff tendon and biceps tendon. In one retrospective study of 100 patients with biceps tendon rupture, there was a nearly twofold increased risk of biceps tendon rupture among statin-treated patients compared to patients not taking statins [51]. And yet,

not all data is so conclusive in identifying a link between statin therapy and tendon rupture. In a multivariate logistic regression model of tendon rupture that controlled for diabetes, renal disease, rheumatologic disease, and steroid use, there was no significant association between statin use and tendon rupture [52]. However, on subgroup analysis, statin exposure was associated with increased odds of tendon rupture in women but not in men.
In addition to statins, other lipid-lowering medications, including niacin and bile acid sequestrants, have also been implicated in producing tendon-related side effects. There are case reports of patients with documented familial hyperlipidemia and Achilles tendon xanthomas who experience new-onset Achilles tendon pain following treatment intensification with niacin and bile acid sequestrants [53]. It has been suggested that these medications may disrupt tissue architecture and stability through the removal of lipids from an existing xanthoma, and that such a phenomenon might explain the tendon pain experienced by some patients.
Finally, in addition to the demonstrated effects of pharmacotherapy on tendon structure and function [46, 47], lipid apheresis therapy in patients with severe familial hyperlipidemia has also been shown to significantly decrease tendon thickness by 18.8 % over a 3-year period [54].

Summary & Future Directions

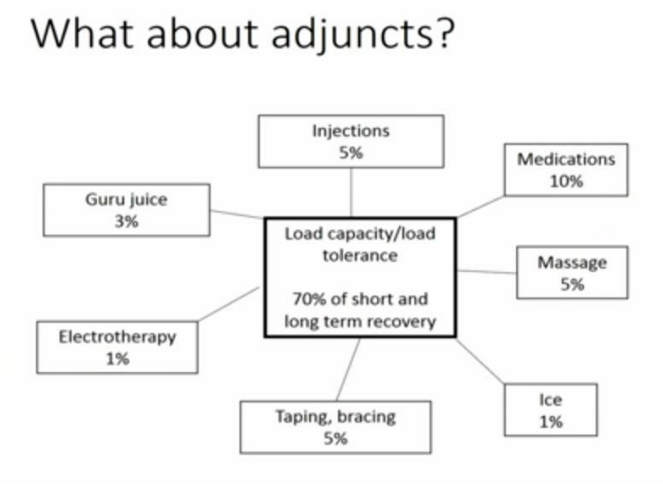
Hypercholesterolemia is an important clinical problem and is associated with significant tendon pathology. Lipid-related tendon pathology is most prevalent among patients with familial dyslipidemias; however, associations between hypercholesterolemia and tendinopathy have also been identified in patients without familial hypercholesterolemia. Rotator cuff tear and Achilles tendon rupture are clearly associated with metabolic derangements, and elevated total cholesterol is sometimes (but not always) among the specific metabolic parameters implicated in patients with tendon pathology.

In injured and healing tendon, the detrimental effects of hypercholesterolemia have also been demonstrated. In healing tendon, high cholesterol environments have been associated with decreased maximum tendon stress and decreased tendon stiffness, and these changes occur after long-term (rather than short-term) exposure to high cholesterol.

The effects of lipid-lowering pharmacotherapy on tendon were also discussed. Statins help to normalize tendon thickness in some patients affected by tendon xanthomas; however, statin therapy has also been implicated as the cause of new-onset tendon pain and as a risk factor for tendon rupture. Statin therapy was shown to improve tendon healing in a rat model with increased tendon max load and increased tendon stiffness. Mechanisms by which statin therapy may alter tendon homeostasis have also been identified. These mechanisms include: changes in cell migration; cell

rounding; mRNA expression for matrix proteins; BMP-2 expression; gap junction communication; and signaling within the COX2/PGE2 pathway. Tendon Homeostasis in Hypercholesterolemia - Louis J. Soslowsky and George W. Fryhofer in Ackermann 2016 ch 14>>

Extra toevoegingen



(Cook 2017)

29

<< ESWT and injections don't change the structure but the nerves.
Cook - 2017 - https://www.youtube.com/watch?v=-kKzoi8Zrik>>

<<Tendinopathy rarely improves long term with only passive treatments such as massage, therapeutic ultrasound, injections, shock-wave therapy etc. Exercise is often the vital ingredient and passive treatments are adjuncts. Multiple injections in particular should be avoided, as this is often associated with a poorer outcome. Please note that these are general principles and there are instances when adjuncts, including injections and surgery are very appropriate in the management of tendinopathy. Dr. Peter Malliaras blog Physio Network>>

Warmte

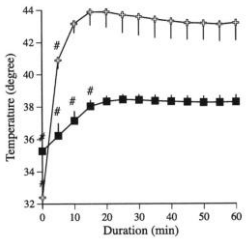


Fig. 3.2 The time course change in the temperatures of muscle (*closed square*) and skin (*open cross*) during 60 min of heating (Modified from Kubo et al. 2012). # significantly different from the point of 60 min

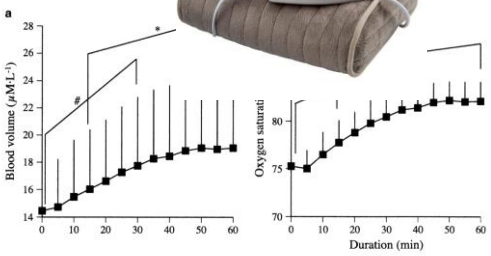


Fig. 3.3 The time course change in the blood volume (**a**) and oxygen saturation (**b**) of the Achilles tendon during 60 min of heating (Modified from Kubo et al. 2012). * significantly different from the resting level. # significantly different from the point of 60 min

spier

pees

30

<<During a 60-min heating, the blood volume and oxygen saturation of the tendon increased significantly from the resting level, and continued to increase by 35 min. These changes in blood circulation of tendon were considerably different from the temperatures of muscle and skin.
It is well known that heating and acupuncture treatments were quite effective in the management of tendon injuries.

Although the mechanisms, which resulted in the increase of blood volume of tendon during heating, are unknown, it seems reasonable to suppose that increase in blood volume of tendon would result from opening of vessels and increase in capillary permeability. In addition, increased oxygen saturation during heating would be related to lower oxygen consumption of tendon [Boushel 2000, Kubo 2008]. Giombini et al. [Giombini 2007] suggested that increases in oxygen and nutrients are necessary to effect tissue repair. Consequently, it is likely that the duration of heating more than 35 min would be able to supply sufficient blood and oxygen to treat the injured tendons. According to previous finding [Giombini 2007], heat treatment was quite effective in the management of tendon injuries, especially overuse tendinopathies.

Indeed, previous study indicated that synthesis and proliferation of collagen were

closely related to oxygen availability [La Van 1990]. Considering the present and these previous findings, we may say that the duration of heating more than 35 min would be necessary to treat the injured tendons.
Kubo in Ackermann 2016>>

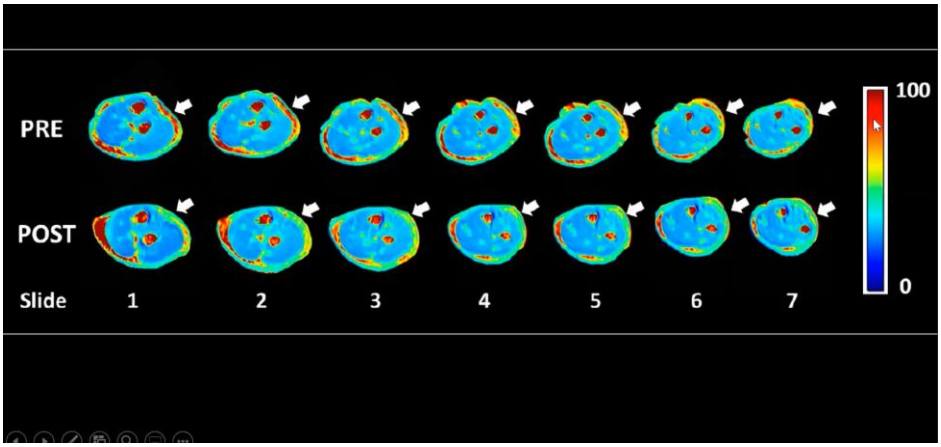
Liquify the fascia

- Betere verglijden tussen fasciculi
- Bevorderen lymfedrainage
- Verbeteren spierfunctie door de-activatie triggerpoints

31

<<Similarly, foam rolling (tool-assisted massage of myofascial tissues) seems to improve short-term flexibility and recovery from muscle soreness [James 2018, Schroeder 2015] and decrease latent trigger point sensitivity.[Wilke, in press] Nevertheless, the physiological mechanisms of these reported effects remain unclear, although initial evidence suggests increases in arterial perfusion, enhanced fascial layer sliding and modified corticospinal excitability following treatment [Aboodarda 2018, Hotfiel 2017, Krause submitted, 2018]. Finally, manual therapies, such as massage, osteopathy or Rolfing (a massage technique based on achieving symmetrical alignment of the body), are frequently used to improve fascial tissue regeneration or athletic performance, although their efficacy still remains to be validated. [Franke 2014, Jacobson 2011] Zügel 2018>>

Effect behandeling



32

Fascial manipulation

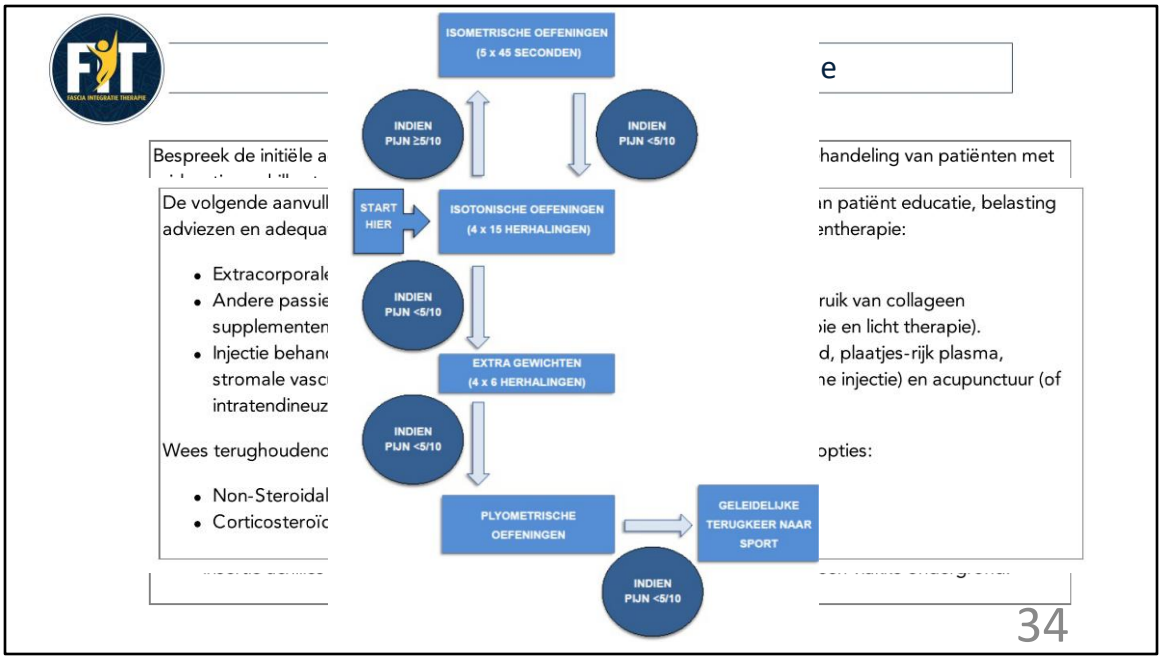
Eighteen patients - patellar tendon pain.
Pain before: VAS 67.8/100
Pain after: VAS 26.5/100
Pain at 1 month: VAS 17.2/100

Results showed a substantial decrease in pain immediately after treatment ($p<0.0001$) and remained unchanged or improved in the short term.

Only treatment of Q-ceps

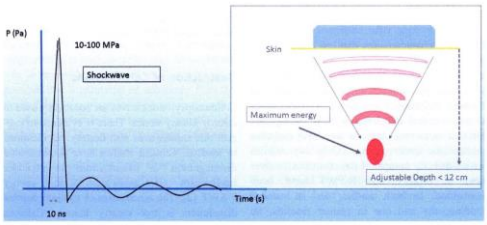
33

Eighteen patients suffering from patellar tendon pain were treated with the Fascial Manipulation technique. Pain was assessed before (VAS 67.8/100) and after (VAS26.5/100) treatment, plus a follow-up evaluation at 1 month (VAS 17.2/100). Results showed a substantial decrease in pain immediately after treatment ($p<0.0001$) and remained unchanged or improved in the short term.
The results show that the patellar tendon may be only the zone of perceived pain and that interesting results can be obtained by treating the muscular fascia of the quadriceps muscle, whose alteration may cause motor incoordination and subsequent pathology.

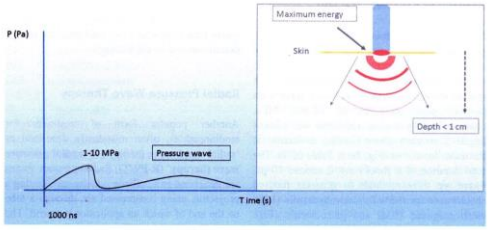


- Shared Deciscion Making
- Duidelijke voorkeur voor oefentherapie, blijkt ook uit onderzoek van Cook.
- Hands-onn (frictie massage) wordt geadviseerd als één van de vele modaliteit als aanvulling op de oefentherapie en in principe alleen als er onvoldoende resultaat geboekt wordt.
- 8 december info avond over de nieuwe richtlijn vanuit KNGF en sportfysio congres

Shockwave



Focussed shockwave



Radial pressure wave

35

<<Shockwave treatments are commonly used in the management of tendon injuries and there is increasing evidence for its clinical effectiveness. There is a paucity of fundamental (in vivo) studies investigating the biological action of shockwave therapy. Destruction of calcifications, pain relief and mechanotransduction-initiated tissue regeneration and remodeling of the tendon are considered to be the most important working mechanisms. The heterogeneity of systems (focussed shockwave therapy vs. radial pressurewave therapy), treatment protocols and study populations, and the fact that there seem to be responders and non-responders, continue to make it difficult to give firm recommendations with regard to the most optimal shockwave therapy approach. Specific knowledge with regard to the effects of shockwave therapy in patients with metabolic tendon disorders is not available. Further fundamental and clinical research is required to determine the value of shockwave therapy in the management of tendinopathy.

Over the past 20 years, shockwave therapy (SWT) has become a popular treatment method for chronic tendon disorders. There is growing evidence for the effectiveness of SWT when treating both upper limb tendinopathies including calcific rotator cuff tendinopathy [Riley 2008, Bevan 2007] and common extensor tendinopathy [Butler 2004], and lower limb tendinopathies including greater trochanteric pain syndrome,

patellar tendinopathy, Achilles tendinopathy and plantar fasciopathy [Butler 2004, Thorpe 2010, Clegg 2012].

Furthermore, the exact working mechanism of shockwaves on (pathologic) tendons has not been elucidated so far. There even seem to be responders and non-responders to shockwave treatment, based on different biological reactions to treatment between individuals [Teunis 2014], which may help to explain why shockwave treatment does not improve symptoms in all patients. Zwerver in Ackermann 2016 Ch 25>>

Extra therapeutische opties

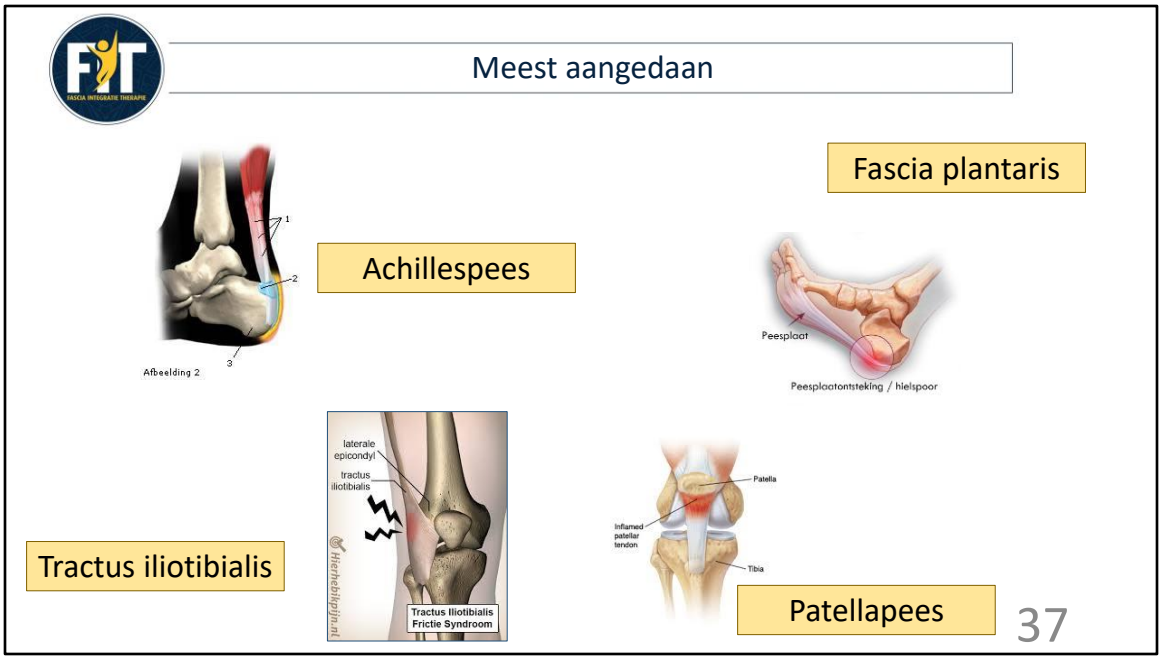
Geen rust maar toename functionele belasting

- Behandeling van de hele keten / TrP's
- Liquify the fascia / IASTM
- Go Slow with the Flow
- Anti-inflammatoire voeding
- Anti-inflammatoir stretchen

36

<<Instrument assisted soft-tissue mobilization for PF
Looney et al. (2011) have reported on a case series in which 10 individuals with plantar fasciitis were treated with soft tissue mobilization methods, involving use of Graston® instruments (see Ch. 12). The protocol was as follows:
Patients received a maximum of 8 treatments over 3-8 weeks, with 1-2 sessions weekly
Focus was on the triceps surae, soleus, plantar fascia, and medial calcaneal tubercle, which were assessed in order to identify local fibrous adhesions
Deeper pressure - using the Graston instruments - was then applied for 1-2 minutes to these areas
Static stretching of the triceps surae, soleus, and plantar fascia, for 30 seconds each was repeated twice
Ice was applied to the plantar region for 15-20 minutes
Home stretching was recommended 3x daily.
Seventy percent of the patients experienced statistically significant and clinically meaningful improvements in pain and function.
Stretching methods and PF .A number of studies have reported on benefits deriving from different forms of stretching in treatment of PF:
DiGiovanni et al. (2003) treated 101 patients with PF of at least 10 months' duration.

All received soft insoles. Half of the patients were taught non-weight-bearing self stretching of the plantar fascia, and the other half were taught stretching of the Achilles tendon/ calf Outcomes after 8 weeks indicated major benefits for the fascia stretching group. At a 2-year follow-up (DiGiovanni et al. 2007), it was found that there had been continued improvement for the plantar fascia-stretching group, where calf muscle stretching had also been employed - with 92% reporting total satisfaction or satisfaction with minor reservations.; and 77% reporting no limitation in their recreational activities. The protocol for plantar self-stretching involved the patient seated, knee flexed, and palpating with a thumb to locate areas of plantar tension. With the thumb in contact with a 'tight' area, the patient was required to dorsiflex the foot to produce 'a sense of stretch', for 10 seconds, repeated 10 times, three times daily. The protocol for calf/Achilles self-stretching involved the patient standing, knee extended, and introducing a mild stretch to the calf for 10 seconds, 10 times, 3 times daily.
Key Point .
Clinical outcomes following manual therapy interventions involving PF, point to benefit deriving from stretching local plantar fascia, in addition to calf and Achilles areas. Local soft-tissue mobilizafion methods (instrument assisted) were also found to be helpful, as was the positional release method, strain-counterstrain Chaitow 2014>>

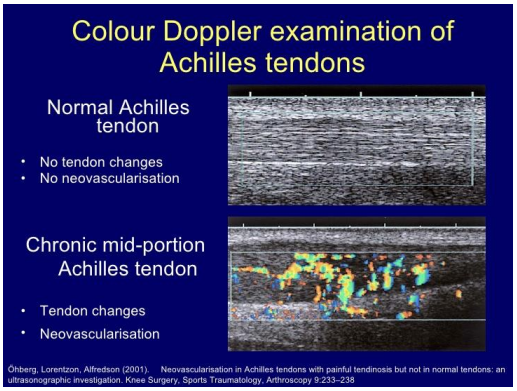


<<Chronic tendon/ligament disorders are highly debilitating and increasingly prevalent [Riley 2008], accounting for one-third of all primary-care musculoskeletal consultations in the UK [Bevan 2007]. Injuries to ligaments, joint capsules and tendons account for approximately 50 % of the 23 million musculoskeletal injuries that occur in the USA annually [Butler 2004]. They affect sporting and sedentary individuals [Riley 2008] in addition to animals such as horses [Thorpe 2010, Clegg 2012]. However, there are no effective treatments or prevention strategies for these injuries [Clegg 2012, Kingma 2007], as a result of limited understanding of the tissues and the aetiology of injury.

The prevalence of tendon injuries is thought to be increasing due to both increasing sports participation as well as an ageing population [Riley 2008]. In particular, increasing age has been demonstrated to be a risk factor for a number of different tendinopathies. A recent systematic review of rotator cuff diseases has identified a prevalence of 9.7 % in patients 20 years or younger, rising to 62 % in patients 80 years or older [Teunis 2014]. A separate report identified that rotator cuff tears affected 40 % of individuals older than 60 years in the USA [8]. Achilles tendinopathy is most commonly observed in the fourth and fifth decade of life [Hess 2010]. Another study identified Achilles, patellar and quadriceps tendon rupture as injuries of middle age, with rotator cuff tears and biceps tendon rupture occurring more frequently in old

age [Clayton 2008]. In the horse, a species which frequently suffers from tendinopathy (Fig. 24.1), a number of studies have demonstrated an association between increasing age and risk of tendon injury [Kasashima 2004, Perkins 2005, Reardon 2012]. Birch in Ackermann 2016 Ch 25>>

Achilles tendinopathy



38

<<The Achilles tendon, the sole of the foot and the longitudinal and transverse arches of the foot store a considerable part of the forces involved when the foot is set down and then release these elastically with the next step. It is therefore important, from a functional point of view, to keep the elasticity of the structures of the sole of the foot mobile and relaxed. Meert 2012>>

<< Khan Khan et al. (1999) described tendinosis as 'tendon degeneration without clinical or histological signs of an inflammatory response, often associated with ageing, micro-trauma and vascular compromise'. Maffulli et al. (2003) characterise tendinosis as a failed healing response. Histologically the type 1 collagen fibres separate and lose their parallel orientation and a greater number of reparative type 3 collagen fibres are found.

Joseph and Denegar (2015) identify intrinsic and extrinsic factors that lead to the development of tendinopathy or rupture. Advancing age and gender, namely men, genetics, and limb mechanics are the intrinsic factors and extrinsic factors include activity level, footwear, training technique, and surface type for both Achilles and patella tendinopathy. They identify loading history but point out that the threshold of overload is still currently poorly understood and that, 'the quantification of

appropriate load (volume, intensity, and frequency) for optimal tendon function remains elusive.'

Importantly Joseph and Denegar point out the fact that appropriate load on tendons is anabolic / constructive at the cellular level, and overloading is catabolic / destructive to tendon tissue. They highlight the seemingly contradictory benefit seen with eccentric exercise. Adding load to a tendinosis which is a degenerative tendon is 'counterintuitive,' but the tenocyte (the tendon constructing cell) may well be stimulated anabolically by eccentric exercise and create its positive response, though, they point out, not in all cases. A certain percentage of those undergoing eccentric training for tendinosis fail and this group may end up with a surgical repair.

Tendonosis does not have to be painful which is why sometimes an Achilles tendon can rupture with no warning. So a seemingly healthy tendon ruptures and the surgeon repairing it finds the tendon markedly degenerative.

Cook and Purdum (2009) have suggested a Continuum model with 3, probably overlapping, stages. These are: reactive tendinopathy, tendon disrepair (failed healing) and degenerative tendinopathy. 'Reactive tendinopathy is proposed to occur in response to acute overload and is described as a noninflammatory proliferative response.
Tendon disrepair resembles the initial stage of reactivity but with greater matrix disorganisation, neovascularity and neuronal ingrowth and represent an aspect of attempted but failed repair', say Joseph and Denegar, and suggest that 'evidence exists that the tendon can recover in form and function from this stage with appropriate treatment inclusive of load modulation and eccentric exercise stimulus. Degenerative Tendinopathy - tendinosis - is thought to be largely irreversible.'

In the clinic Joseph and Denegar divide this 3 part continuum into 2 e an 'acute reactive' and 'late degenerative' phase and suggest that the 2 phases may require different approaches in treatment. With the acute reactive phase requiring decreased tendon stress (decreased intensity of exercise, relative rest and increased rest periods) and perhaps non steroidal anti-inflammatory drugs (NSAID's), not to control inflammation, but for their ability to control the over proliferation of prostaglandins and ground substance.
Steroids might convey short term pain relief but increase risk of rupture. So their use needs careful consideration, they suggest. The late degenerative phase focus of treatment could include eccentric exercise and extracorporeal shockwave therapy (ESWT).

Achilles tendon injury diagnosis is reported by Cook et al. (2002) as being one of the 'simpler clinical diagnosis to make' as the change in activity levels that often precede

the start of the pain is often remembered. The Achilles tendon needs, from the first step out of bed in the morning, to work in almost full range e which means that morning pain is a hallmark of the condition. In McNeil, 2015>>

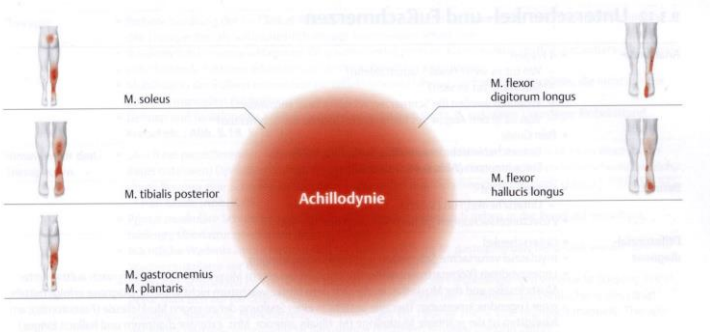
The ankle being plantarflexed before heel strike means that as the forefoot strikes the ground, the triceps surae will be eccentrically loaded (where they are at their strongest) and, interestingly, it is eccentric loading that is missing from the gait cycle if someone rearfoot strikes. Could there be a correlation between a lack of forefoot striking and Achilles tendinopathy, after all, since the work of Alfredson (1998), one of the primary methodologies for treating tendinopathic injury has been to prescribe an eccentric loading protocol.
Although the Achilles tendon is not inherently vulnerable to injury, it is hurt more often than any other tendon. It has to operate the body's most powerful lever. Like its Greek namesake, the Achilles tendon is no whimp: Not surprisingly, considering the work it has to do, it is the most powerful tendon in the body. When the knee is misaligned an uneven pull is through the calcaneus (Egoscue 1998)

- 52% runners have to deal with an AP injury, in football AP injuries cause the most prolonged outages
- With a 10 km run: 1.69 million kg per leg (4500 N per step)
- There is little relationship between the findings of imaging research / degree of degeneration and pain.
- With degeneration you see hypo-echogenic areas and neovascularization
- But no / little correlation between structural changes and complaints
- No prognostic value of Echo and MRI
- You will find Achilles tendon degeneration in 11-18% of asymptomatic athletes

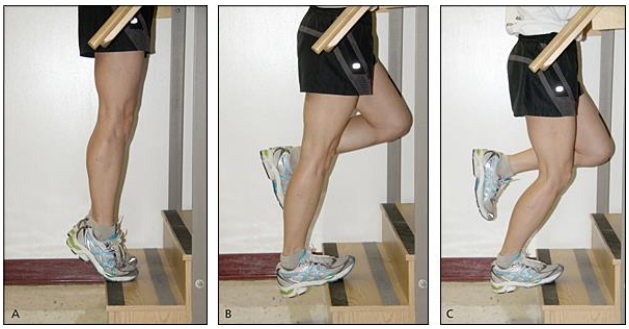
Achillodynie

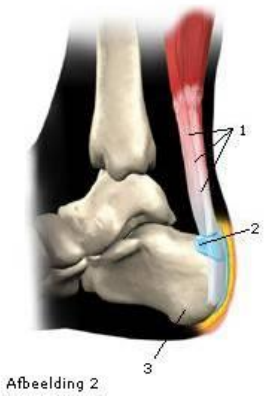
TrP's

Zeer vaak: Soleus, tib post
Vaak: gastroc, plantaris



Achilles pees





Afbeelding 2

40

Acute phase:

- Load management / unloading
- Ibuprofen to reduce cell response

Alfredson has started eccentric training with AP tendinopathies (based on own experience)
150 x / day, 12 weeks, very painful
There are now several (milder) eccentric protocols with the same result.

At midportion tendinopathy: on stairs
With insertion tendinopathy: on the ground (otherwise too much compression on the attachment)
50-60% result, the mechanism is unclear

<<Heavy-load eccentric calf training for mid-portion Achilles tendinopathy in most studies is carried out according to a protocol initially described by Alfredson et al. (1998). The patient is standing with his or her forefoot on the edge of a stepper or stairs (Figure 7.2). Body weight is initially supported by both legs in full plantar flexion of the foot. The calf muscles of the injured leg are then eccentrically loaded by

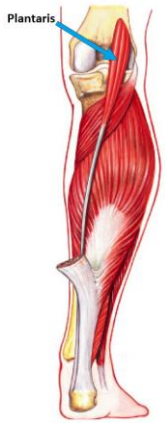
lowering the heel with the knee straight or bent to load the gastrocnemii and the soleus, respectively. The non-injured leg is used to get back to the start position. For each exercise (knee bent or straight), 3 sets of 15 repetitions are performed. Patients are told to tolerate muscle soreness and to stop only when pain becomes disabling. Additionally, patients are instructed to progressively increase load by using a backpack loaded with weights whenever muscle soreness makes this tolerable. This protocol has been shown to be 89 per cent satisfactory in 101 recreational athletes with mid-portion Achilles tendinopathy. Success was only 32 per cent in patients with insertional Achilles tendon pain (Fahlstrom et al, 2003). A comprehensive meta-analysis of the literature, complemented by semi-structured interviews, provides strong evidence for the effectiveness of this type of eccentric exercise, with shockwave therapy also being effective for the treatment for mid-portion Achilles tendinopathy (Rowe et al, 2012). Eccentric exercise has been shown to increase collagen synthesis rate in the injured Achilles tendon, but not in the contralateral uninjured tendon (Langberg et al, 2007). However, this does not directly explain the mechanisms responsible for clinical improvement. MRI imaging has been found to be a useful adjunct to monitor clinical outcome and morphological response of eccentric rehabilitation programmes (Shalabi, 2004). This study found tendon volume to decrease by 13 per cent and intratendinous signal by 23 per cent after 12 weeks of eccentric calf muscle training. There was a significant correlation between the change in signal intensity and reduction in pain, but not between the change in volume and pain reduction. Clinical parameters, as well as MRI findings, showed further improvements in a 4.2 years follow-up study, even when therapy was discontinued (Gardin et al, 2010). Hopeler 2015>>

Attachment: more soil substance to absorb the compression forces that occur with dorsal flexion

Insertion tendinopathy: first 2 cm do not do the exercise on the stairs because then you will get too much compression on the attachment

Bij geen resultaat

- ESWT
- Prolotherapie
- High Volume injecties
- Verwijderen plantarispees
- EPTE (Percutane Electrolyse Therapie)
- Verwijderen paratenon
- Debridement Achillespees



41

<<Spang C, Alfredson H, Docking SI, Masci L, Andersson G. The plantaris tendon: a narrative review focusing on anatomical features and clinical importance. Bone Joint J. 2016 Oct;98-B(10):1312-1319.
In recent years, the plantaris tendon has been implicated in the development of chronic painful mid-portion Achilles tendinopathy. In some cases, a thickened plantaris tendon is closely associated with the Achilles tendon, and surgical excision of the plantaris tendon has been reported to be curative in patients who have not derived benefit following conservative treatment and surgical interventions. The aim of this review is to outline the basic aspects of, and the recent research findings, related to the plantaris tendon, covering anatomical and clinical studies including those dealing with histology, imaging and treatment.>>

Patellapees

- Pijn onderpool patella
- Pijn toename bij zwaardere belasting, mn bij energy storing
- Pijn weg zodra de belasting stopt, meestal geen pijn in rust

Research: Level 1 evidence: treating the hip

42

<< Patellar tendinopathy, as one of many potential diagnoses producing anterior knee pain, has specific and defining hallmark clinical features32,55 that consist of (1) pain localized to the inferior pole of the patella11 and (2) load-related pain that increases with the demand on the knee extensors, notably in activities that store and release energy in the patellar tendon.57,77 Other signs and symptoms, such as pain with prolonged sitting, squatting, and stairs, may be present but are also features of patellofemoral pain (PFP) and potentially other pathologies. Tendon pain occurs instantly with loading and usually ceases almost immediately when the load is removed.75 Pain is rarely experienced in a resting state.75 Pain may improve with repeated loading (the “warm-up” phenomenon),55,75 but there is often increased pain the day after energy-storage activities.75 Clinically, it is noted that dose-dependent pain is a key feature, and assessment should demonstrate that the pain increases as the magnitude or rate of application of the load on the tendon increases.55 For example, pain should increase when progressing from a shallow to a deeper squat, and from a smaller to a greater hop height.

Studies have suggested that up to 24 hours of pain provocation after energy-storage activities may be acceptable during rehabilitation(Konsgaard 2009, Silbernagel 2001) so here we will define “irritable” tendon pain as pain provocation of greater than 24

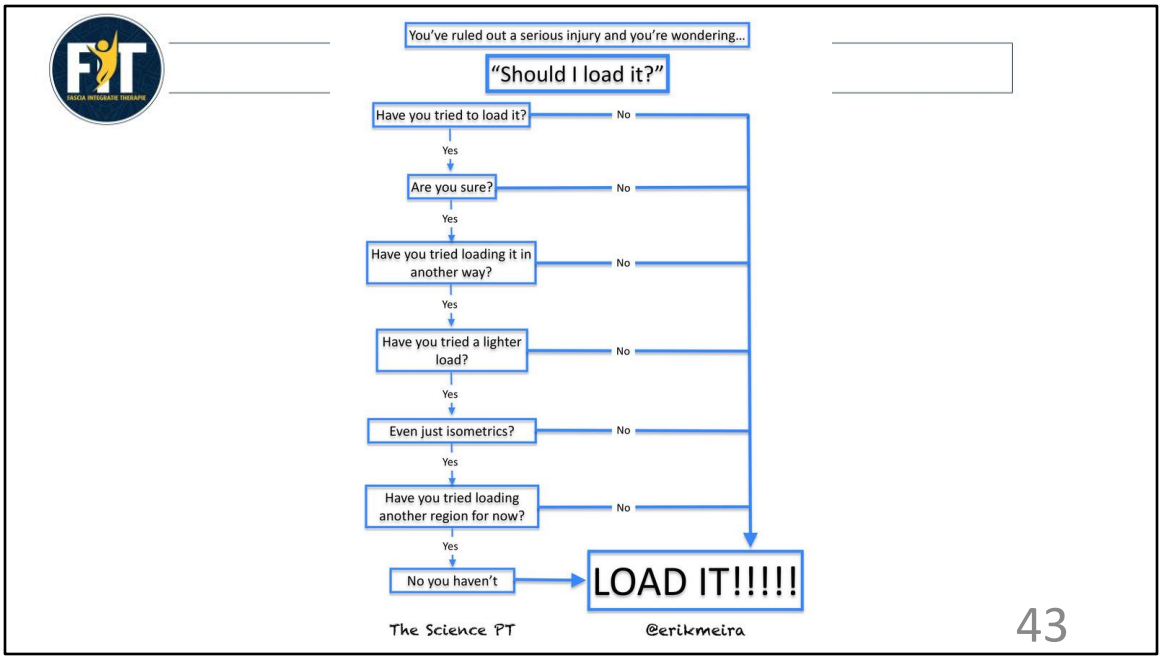
hours, and “stable” tendon pain as settling within 24 hours after energy-storage activities.

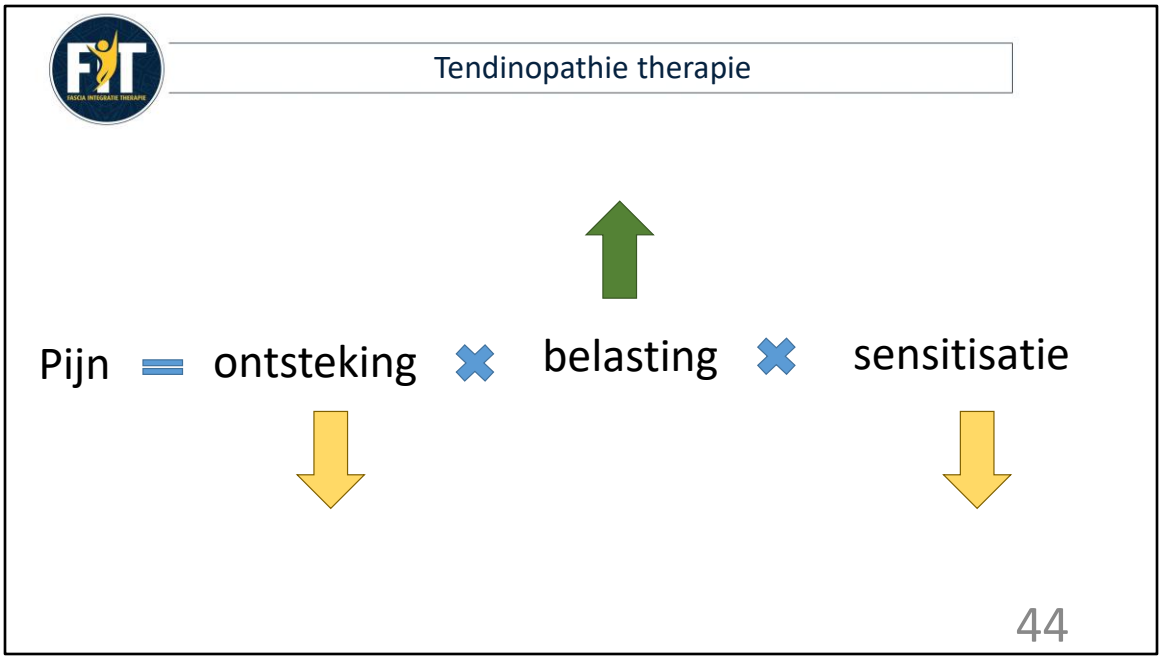
A thorough examination of the entire lower extremity is necessary to identify relevant deficits at the hip, knee, and ankle/foot region. Atrophy or reduced strength in antigravity muscles, including the gluteus maximus,55 quadriceps,22 and calf,55 is often observed by the authors,
Foot posture/ alignment,22,24 quadriceps and hamstring flexibility,95 as well as weight-bearing ankle dorsiflexion range of motion4,62 have been associated with patellar tendinopathy and should also be assessed.

The clinical experience of the present authors suggests that athletes with patellar tendon pain tend to reduce the amount of knee flexion and appear stiff in their landing. Regardless of the individual strategy, it is optimal to try to distribute load through the entire kinetic chain, and the purpose of evaluating function (including hopping and landing) is to identify deficits that need to be addressed as part of rehabilitation.

Patellar tendon imaging does not confirm patellar tendon pain, as pathology observed via ultrasound imaging may be present in asymptomatic individuals.61 Accordingly, serial imaging is not recommended, as symptoms often improve without corresponding changes in pathology on ultrasound imaging or magnetic resonance imaging (MRI).27,60

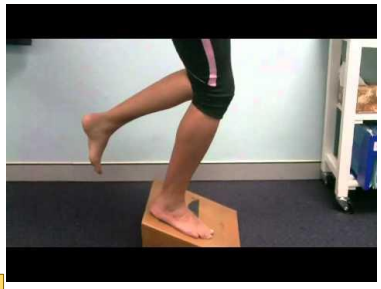
Aside from the inferior pole of the patella, tendinopathy of the extensor mechanism of the knee can occur at the quadriceps tendon or distal insertion of the patellar tendon at the tibial tuberosity. These less common clinical presentations also have unique features. Quadriceps tendinopathy is characterized by pain localized to the quadriceps tendon32 and, in the authors’ experience, is often associated with movements requiring deep knee flexion, such as those performed by volleyballers and weight lifters.72 Distal patellar tendon pain, often seen in distance runners, is localized near the tibial tuberosity.32,78 Malliaras 2015>>


You've ruled out a serious injury and you're wondering...
"Should I load it?"
Have you tried to load it?
No
Yes
Are you sure?
No
Yes
Have you tried loading it in another way?
No
Yes
Have you tried a lighter load?
No
Yes
Even just isometrics?
No
Yes
Have you tried loading another region for now?
No
Yes
No you haven't
LOAD IT!!!!!
The Science PT
@erikmeira



To reduce pain for many patients (and therapists) reduction of load is the first thing they will try. Right after an injury that is a good choice but after the recovery phase it is not! Loading is crucial for optimal recovery so reduction of inflammation and reduction of sensitisation should be the first treatment targets.

Behandeling



- Assessment hele keten (FFO)
- De-activeer triggerpoints
- Mobilisatie pees (liquify the fascia)
- Training (traag en zwaar)
- Isometrisch (5x45 sec 3x/dag)
- Spring en land oefeningen
- ESWT / Tecartherapie
- Voeding
- Versterken immuunsysteem

45

<< The authors of a recent systematic review determined that there was limited evidence supporting the decline squat program and moderate evidence supporting the Heavy Slow Resistamnce (HSR) program. [Malliaras 2013]

It is the authors' opinion that pain assessment based on a standard load test for each individual is more important than a pain rating during exercise to determine the progression of loading through the course of the rehabilitation.

Isometric Loading Five repetitions of 45-second isometric mid-range quadriceps exercise at 70% of maximal voluntary contraction have been shown to reduce patellar tendon pain for 45 minutes after exercise. The exercise dosage depends on individual factors, but evidence and clinical experience indicate 5 repetitions of a 45-second hold, 2 to 3 times per day,18,74 with 2 minutes of rest between holds to allow recovery. It is important that there be no muscle fasciculation during the isometric exercises, as this may be perceived to indicate that the load is too high.

Rehabilitation of patellar tendinopathy can be a slow and frustrating process, both for the athlete and clinician.

Bahr and Bahr [Bahr 2014] investigated long-term outcome after eccentric training to manage patellar tendinopathy and determined that only 46% (6/13) of athletes had returned to full training and were pain free at 12 months.

In the authors' experience, poor baseline neuromuscular function, muscle atrophy, pain irritability, as well as multiple prior intratendinous interventions (eg, platelet-rich plasma or other injections) appear to be associated with longer rehabilitation times.

Athletes with patellar tendinopathy may require progressive jump-land retraining. The strategies of landing with a stiff knee9,29,89 and moving into hip extension rather than hip flexion (in a horizontal jump)29 have been associated with higher patellar tendon injury. Landing kinematics can be retrained, focusing on soft landings on the forefoot-midfoot region, with greater ankle, knee, and hip range of motion,69 to reduce the magnitude of peak vertical ground reaction forces and peak loading rates.25

The authors have found that isometric exercises (eg, seated knee extension, Spanish squat holds) are most effective at managing pain and can be performed several times daily, as described under stage 1 of the rehabilitation process.

Selected adjunct interventions, which may include nonsteroidal anti-inflammatory drugs or corticosteroids (taken orally or with a peritendinous injection)18 in difficult cases, can be very useful in reducing symptoms to allow load progression within a controlled rehabilitation program.
Malliaras 2015>>

<<Interventions for fascial tissue pathologies in sports medicine Fascial tissue dysfunction in the field of sports medicine is rarely treated surgically. Anti-inflammatory drugs are used for sports-related overuse pathologies; however, they may impair regeneration and diminish tissue adaptation. [Mackey 2007, Christensen 2011] Gyrase-inhibiting antibiotics often contribute to an increased likelihood of tendon injuries in sports.[Lewis 2014] In addition, injections of platelet-rich plasma seem to be successful in some cases of tendinopathy, although efficacy remains inconclusive. [James 2018, Wilke in press] Moderate evidence exists on the value of shockwave therapy and eccentric loading in tendon healing. Speed 2014, Douglas 2017] Similarly, foam rolling (tool-assisted massage of myofascial tissues) seems to improve short-term flexibility and recovery from muscle soreness [James 2018, Schroeder 2015] and decrease latent trigger point sensitivity.[Wilke, in press] Nevertheless, the physiological mechanisms of these reported effects remain unclear, although initial evidence suggests increases in arterial perfusion, enhanced fascial layer sliding and modified corticospinal excitability following treatment [Aboodarda 2018, Hotfiel 2017, Krause submitted, 2018]. Finally, manual therapies, such as

massage, osteopathy or Rolfing (a massage technique based on achieving symmetrical alignment of the body), are frequently used to improve fascial tissue regeneration or athletic performance, although their efficacy still remains to be validated. [Franke 2014, Jacobson 2011]
Outlook and perspectives for future research: Hopefully, current and future improvements in assessment methodologies will generate more conclusive research regarding which treatment modalities are most promising for specific conditions. While commercial and other interests often favour the promotion of premature positive conclusions about specific fasciarelated treatments, strict application of scientific rigour is essential for the development of this promising field. Zügel 2018>>

The effect of eccentric training with patella tendinopathy is less clear than with AP tendinopathy

<<The treatment strategy for patellar tendinopathy (colloquially, "jumper's knee") is very similar to that of the Achilles tendon. A prospective randomized study involving 35 patients and 40 knees with grade-llIB patellar tendinopathy compared primary surgical treatment to eccentric training (Bahr et al, 2006). Surgical treatment consisted of a full-thickness, wedge-shaped excision of abnormal tissue, followed by a structured rehabilitation programme including eccentric training. The eccentric programme was an adaptation of the Alfredson et al. (1998) protocol for the Achilles tendon, discussed above. It consisted of three sets of 15 squats performed on a 25° incline board twice daily (Figure 7.3). The squat was executed with the back vertical and to a knee flexion of 90°. Initially, the eccentric part of the squat was performed with the injured knee, and the upward movement with the healthy knee. The patients were instructed to tolerate all but disabling pains and to add weight in a backpack when the pain decreased to <3 on a visual analogue scale (with 0 representing no pain and 10 representing the worst possible pain). If pain increased to >5, weight was reduced. Eccentric training was performed for 12 weeks. After four weeks, patients were allowed to cycle and jog on flat surfaces and to exercise in water when these activities did not cause pain. The treatment effect was assessed using the VISA (Victorian Institute for Sport Assessment) score, with a possible range fi-om 0 to 100. After 12 months, the VISA score improved similarly for the surgically treated and the eccentrically trained group from 30 to 70. In the surgically treated group, 5 knees were free of symptoms, 12 were improved, 2 were unchanged and 1 got worse. In the eccentric training group, seven knees were free of symptoms, eight were improved and five were unchanged. The knees that did not respond to eccentric exercise underwent secondary surgery after three to six months. Bahr et al. (2006) conclude that patellar tendinopathy should be treated with eccentric training for minimally three months before considering surgical treatment. A review of seven prospective studies using different eccentric protocols for patellar tendinopathy proposed that treatment should comprise a decline board, that exercise should elicit

some degree of discomfort and that athletes should be removed from sports activity (Visnes and Bahr, 2007). A more recent study questions the evidence that athletes need t be withdrawn from sport (Saithna et al, 2012). A randomized contolled and single blind trial compared the effects of peritendinous corticosteroid injections to eccentric decline training and slow heavy resistance training as treatment in patellar tendinopathy (Kongsgaard et al, 2009). Cortisone treatment was found to have good short-term results, but lacking long-term clinical improvements. Resistance training had better results than eccentric training after six months, and further showed elevated collagen network turnover.

Overall, the treatment situation in patellar tendinopathy is very similar to that of Achilles tendinopathy, with eccentric exercise being the established first-line treatment of these conditions. Shockwave therapy, sclerosing injections and microsurgery may be used when eccentric exercise alone for at least three months does not yield satisfactory results. Surgical treatment is considered when the less invasive treatment modalities are exhausted, but is not recommended as a first option in any condition. Hopeler 2015>>

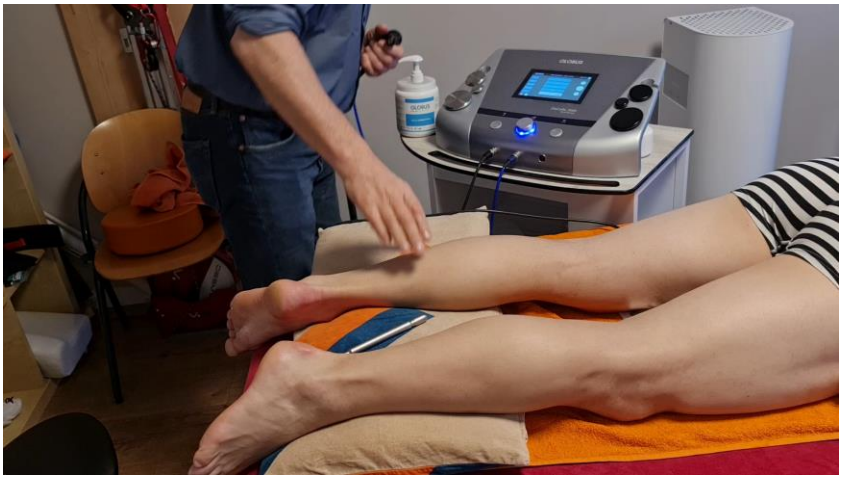
<< Rio E, Kidgell D, Purdam C, Gaida J, Moseley GL, Pearce AJ, Cook J. Isometric exercise induces analgesia and reduces inhibition in patellar tendinopathy. Br J Sports Med. 2015 Oct;49(19):1277-83. doi: 10.1136/bjsports-2014-094386. Epub 2015 May 15.
CONCLUSIONS:
A single resistance training bout of isometric contractions reduced tendon pain immediately for at least 45 min postintervention and increased MVIC. The reduction in pain was paralleled by a reduction in cortical inhibition, providing insight into potential mechanisms. Isometric contractions can be completed without pain for people with PT. The clinical implications are that isometric muscle contractions may be used to reduce pain in people with PT without a reduction in muscle strength.>>

<< Rio E, van Ark M, Docking S, Moseley GL, Kidgell D, Gaida JE, van den Akker-Scheek I, Zwerver J, Cook J. Isometric Contractions Are More Analgesic Than Isotonic Contractions for Patellar Tendon Pain: An In-Season Randomized Clinical Trial. Clin J Sport Med. 2016 Aug 10. [Epub ahead of print]
CONCLUSIONS:
Both protocols appear efficacious for in-season athletes to reduce pain, however, isometric contractions demonstrated significantly greater immediate analgesia throughout the 4-week trial. Greater analgesia may increase the ability to load or perform.>>

Of in het kort

46

casus



47

Of in het kort

48