CURRENT OPINIONS ON TENDINOPATHY

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Abstract

Introduction: Tendinopathy is characterized by pain in the tendon and impaired performance sometimes associated with swelling of the tendon. Its diagnosis is usually clinical but ultrasonography and magnetic resonance imaging can refine the diagnosis.

Epidemiology: Tendinopathy is highly prevalent and is one of the most frequently self reported musculoskeletal diseases in physical workers and sports people. Nevertheless, it is very difficult to carry out general epidemiologic studies on tendinopathy because of the varying sports cultures and sports habits in different countries.

Aetiology: The aetiology of tendinopathy seems to be multi-factorial, involving intrinsic and extrinsic factors. The role of inflammation is still debated but the absence of inflammatory cells does not mean that inflammatory mediators are not implicated. Different theories have been advanced to explain pain and chronicity mechanisms, but these mechanisms remain largely unknown.

Treatments: "Conventional" treatments are generally employed empirically to fight pain and inflammation but they do not modify the histological structure of the tendon. However, these treatments are not completely satisfactory and the recurrence of symptoms is common. Currently, eccentric training remains the treatment of choice for tendinopathy, even though some studies are contradictory. Moreover, many interesting new treatments are now being developed to treat tendinopathy, but there is little evidence to support their use in clinical practice.

Keywords: aetiology, epidemiology, inflammation, tendinopathy, therapeutic advances, treatments

Introduction

Musculoskeletal diseases are a heterogeneous group of conditions. The description and definition of different musculoskeletal diseases will differ, between medical specialists and the general population, and also between different cultures and languages. Self reported musculoskeletal diseases are highly prevalent and are estimated at between 2% and 65% (depending on survey design factors and the age of the study population) (Forde et al., 2005). The number of overuse injuries is not exactly known, but in sports medicine, they account for 30 to 50% of all injuries (Scott and Ashe, 2006). Generally, for physical workers, the prevalence of musculoskeletal symptoms increases with duration of employment (Forde et al., 2005). Age-adjusted logistic regression analyses have shown that people who have worked for 25 to 35 years are more likely to develop tendinopathy (Forde et al., 2005).

Tendinopathy is a common overuse injury in the athletic and working populations; it is the main reason for consultation for a musculoskeletal complaint, and corresponds to around 30% of all such consultations with a general practitioner (Forde et al., 2005; Riley, 2008). Secondary referral rates vary widely, but one study reported that 17% of new patients seen in a locomotor clinic had soft-tissue complaints (Riley, 2008).

In the last twenty years, sports activities have become increasingly important in our modern society. Moreover, much attention has been paid to high level athletes in competitive sports, which has increased the demand on sports performance. Unfortunately, this has increased the risk of injuries, especially of overuse injuries, which result from the necessity to train more often, for longer periods of time, and more intensively. Moreover, in leisure sports, there are greater numbers participating, starting younger or continuing for longer, this includes an increasing number of women, who are spending greater amounts of time participating in sports. In more the equipment of these people is not always adapted to the sports person, thus increasing the risk of tendinopathy (Maffulli et al., 2003). Sixty percent of overuse injuries sustained in running are experienced by the male population; women under the age of 30 are at the greatest risk of overuse injuries (Maffulli et al., 2003).

A few years ago the word “tendinitis” was widely employed to designate pain located at the tendon. This term corresponds to a histopathological description of tendon impairment associated with an intratendinous inflammation (Khan et al., 2002; Maffulli et al., 2003). By contrast, “tendinosis” has been employed to describe a histopathological state of degenerative tendon without inflammatory signs or correlation with clinical symptoms (Khan et al., 2002; Maffulli et al., 2003). More recently, this concept has evolved and the word “tendinopathy” has been proposed for the clinical diagnosis of pain accompanied by impaired performance, and sometimes swelling in the tendon (Khan et al., 2002).

Currently, the most employed clinical and functional classification for tendinopathy remains the one proposed by Blazina et al (Blazina et al., 1973). This classification distinguishes 4 stages: 1) pain after sports activity; 2) pain at the beginning of sports activity, disappearing with warm-up and sometimes reappearing with fatigue; 3) pain at rest and during activity; 4) rupture of the tendon. It also seems useful to classify the chronology of symptoms into 3 stages: when symptoms have been present for 0 to 6 weeks, the tendinopathy is characterized as “acute”, between 6 to 12 weeks, it is regarded as “sub-acute” and after more than 3 months, it may be considered as “chronic”.

However Nirschl et al proposed other staging systems and pain phase systems based on the observed histology at the time of surgery for tennis elbow and derived from the patient’s description of the duration and intensity of pain (Table 1) (Nirschl and Ashman, 2003).

The aim of this review is to present a critical analysis of the current opinion on tendinopathy, from physiopathology to treatments.

Histology and physiopathology

Compared with the normal tendon, which is glistening white and has a firm fibroelastic texture, tendinopathy induces specific modifications: the tendon appears grey or yellow-brown and is soft, friable, fragile and thin or oedematous (Nirschl and Ashman, 2003; Scott and Ashe, 2006).

Under light microscopy, tendinopathy shows:

- disrupted collagen with fibres thinner than normal and loss of the classical hierarchical structure (Nirschl and Ashman, 2003; Riley, 2008). Tenocytes located at the site of tendinopathy produce abnormal amounts of collagen III, commonly associated with wound healing (Cook et al., 2002).
- increased ground substance with high concentrations of glycosaminoglycans and proteoglycans. (Sharma and Maffulli, 2005; Rees et al., 2009). This increased proteoglycan turnover is likely required to maintain normal tendon homeostasis, with perturbations in proteoglycan metabolism contributing to tissue dysfunction, resulting in chondrogenic differentiation (de Mos et al., 2009; Rees et al., 2009).
- changes in cellularity with more prominent and numerous tenocytes with more rounded nuclei, and without a fine spindle shape (Cook et al., 2002; Nirschl and Ashman, 2003; Riley, 2008).
- an increase in apoptosis or programmed cell death possibly explained by oxidative stress (Millar et al., 2009) and loss of cellular homeostatic tension (Cook et al., 2002; Egerbacher et al., 2008).
- neovascularization demonstrate on color and power Doppler US, a process which could be associated with tendon repair (Alfredson et al., 2006; Riley, 2008; Ackermann et al., 2009) or chronic pain (Knobloch, 2008). In a recent study, US confirmed neovessels in the majority of Achilles tendinopathy cases but the severity of symptoms was not correlated with a neovascularization score (Sengkerij et al., 2009). Electron microscopy has demonstrated that some vascular buds do not possess a lumen; this granulation-like tissue has been termed angiofibroblastic hyperplasia (Nirschl and Ashman, 2003).

In summary, changes in the tendinous matrix composition are in part mediated by inflammatory mediators and metalloproteinase enzymes and are consistent with changes in cell-mediated matrix remodelling that precede the onset of clinical symptoms, as shown in Fig. 1 (Bard, 2003; Riley, 2008; Cook and Purdam, 2009). Thus, it seems that part of the treatment of tendinopathy should focus on correcting intratendinous modifications.

The aetiology of tendinopathy seems to be a multi-factorial process, involving promoting factors that are intrinsic or extrinsic, working either alone or in combination (Nirschl and Ashman, 2003; Jarvinen et al., 2005; Scott and Ashe, 2006; Fredberg and Stengaard-Pedersen, 2008). Aetiological factors are summarized in Table 1, where we distinguish between innate general factors, acquired general factors and acquired local factors.

In particular, it seems that after repetitive mechanical loads and/or when the load exceeds the strength of the tendon, the tendon can become progressively micro- and macroscopically damaged. Collagen fibres begin to denature, causing progressively a focal area of intratendinous degeneration, partial tears, and ruptures (Bard, 2003; Jarvinen et al., 2005; Sharma and Maffulli, 2005) (Fig. 1). Indeed, excessive load of the lower extremities and training errors have been shown to be present in 60 to 80% of patients who have Achilles tendon overuse injuries (Jarvinen et al., 2005). Regarding blood circulation of a tendon, overuse may cause damage at both the micro- and the macrovasculature (Rees et al., 2006). Impaired metabolic activity including disturbed oxygen transport is likely to be detrimental to molecular cross-linking and tissue repair. The ageing tendon is characterized by a low rate of metabolism, a progressive decrease in elasticity and tensile strength and a decreasing tendon blood flow (Fig. 1 & Table 1); thus, age would be regarded as an important predisposing factor in the occurrence of tendinopathy.

However, contrary to previous articles, a study of Master track and field athletes did not detect any influence of age, gender, weight, height, or impact profile on the development of Achilles tendinopathy (Longo et al., 2009). This conclusion certainly needs to be confirmed.

Although the role of inflammation is still debated (Sharma and Maffulli, 2005; Riley, 2008; Millar et al., 2009), animal and human studies support both the overload theory and the notion that inflammation may play a role in the aetiology of acute tendinopathy. However, a degenerative process soon supersedes this (Rees et al., 2006). More recently, it has been shown that an inflammatory process may be related to the development of chronic tendinopathies (Fredberg and Stengaard-Pedersen, 2008; Millar et al., 2009). The absence of inflammatory cells in or around the lesion does not mean that inflammatory mediators are not implicated in tendinopathies (Rees et al., 2006; Riley, 2008; Millar et al., 2009). Biochemically, endothelial cells express and respond to a

network of inflammatory mediators such as interleukins (IL-1β, IL-6), prostaglandins (PGE1, PGE2), nitric oxide synthetase (NOS), growth factors (PDGF, TGF-β, b-FGF, EGF, VEGF, IGF-1) and other potential modulators of tendon cell activity (glutamate, substance P) (Sharma and Maffulli, 2005; Riley, 2008; Ackermann et al., 2009; Millar et al., 2009). The balance between these growth factors (GFs) may have important implications in the control of tendon healing (Anitua et al., 2007). The GFs also increase the production of COX-2, the expression of cytosolic phospholipase-A2 and the activation of stress-activated protein kinase (Fredberg and Stengaard-Pedersen, 2008). Deposits of fibrinogen or fibrin have also been described in chronic Achilles tendinopathy. Experimental evidence indicates that bioactive peptides released in the formation and degradation of fibrin increase vascular permeability, exerting a chemotactic effect on fibroblasts and inflammatory cells.Tendon integrity depends on the extracellular matrix metabolism, which is regulated by proteolitic enzymes (Karousou et al., 2008). In tendinopathy, there are changes in the expression and activity of various matrix-degrading enzyme metalloproteinases, particularly the collagenases (MMP-1, MP-3, MMP-8, MMP-13) (Sun et al., 2008) and gelatinases (MMP-2, MMP-9) (Orchard et al., 2008). Changes in the level of tissue inhibitors of metalloproteinase (TIMPs), which are consistent with increased proteolytic activity in degenerate tendons, are also reported (Karousou et al., 2008; Riley, 2008). Quinolones enhance interleukin-1-mediated MMP3 release, inhibit tenocyte replication, and reduced collagen and matrix synthesis (September et al., 2009).

One recently-described concept is the ‘cholinergic anti-inflammatory pathway’ and the proliferative and tissue reorganization process via autocrine and paracrine effects that may be implicated in tendinopathy (Forsgren et al., 2009). This concept refers to the occurrence of the immunomodulatory effects of acetylcholine (ACh) released from cholinergic nerves. The neuronal inputs to immune cells thus control cytokine production via an inflammatory reflex. There is an attenuation in the release of TNF-α and other pro-inflammatory cytokines and in macrophage activation, in response to electrical stimulation of the vagus nerve (Forsgren et al., 2009).

Pain mechanisms and causes of chronicity

Surprisingly, the pain mechanism has not been wholly elucidated. Classical theories state that inflammation and its mediators (prostaglandins, thromboxanes, prostacyclines) lead to pain, or in severe chronic forms, pain is due to separation of collagen fibres (Sharma and Maffulli, 2005). Biochemical stimulation of the nociceptors due to extravasation of glucosaminoglycans (chondroitin sulphates) and other biochemical irritants (substance P, glutamate and its receptor NMDAR1) has been suggested in more recent theories (Ackermann et al., 2009). On the other hand, tenocytes produce ACh and immunoreactions are possible with the ACh-receptor M2 of nerve fibres which accompany blood vessels into the pathological tendon (Fredberg and Stengaard-Pedersen, 2008; Knobloch, 2008; Forsgren et al., 2009), yet the presence of neovascularization does not predict pain or functional outcomes (de Jonge et al., 2008). The non-neuronal cholinergic system may be involved in the establishment of a “cholinergic anti-inflammatory pathway”. Newly obtained information suggests that this system plays an important functional role in chronically painful tendons and in inflammatory conditions (Forsgren et al., 2009).

However, evidence of local, non-neuronal production of catecholamines (not ACh), has been recently demonstrated in fibroblasts at the muscle origin of the lateral and medial epicondyles, in patients with tennis and golf elbow. This production of catecholamines might have an influence on blood vessel regulation and pain mechanisms in these conditions (Zeisig et al., 2009).

Nevertheless, chronic pain or repeated tendinopathies could result from the absence of consensus in treatment. Indeed, if the cause of tendinopathy is the inability of the tendon to bear constraints, passive treatments, generally purely analgesic and anti-inflammatory, could remain ineffective. Only active treatments, such as eccentric exercises, or new therapies, such as platelet-rich plasma or extracorporeal shock waves, would have an actual action on structure and adaptation of tendons to stress (Khan and Scott, 2009). Indeed, the term “mechanotransduction” refers to the process by which the body converts mechanical loading into cellular responses which, in turn, promote structural changes (Khan and Scott, 2009). Thus, the process enhances collagen fibril alignment with increased tensile strength, encourages fibroblast activity and collagen cross-linkage formation, and prevents adhesions between the healing tendon and adjacent tissue (Cook et al., 2002; Stasinopoulos et al., 2005; Petersen et al., 2007; Barone et al., 2008). Another cause of

tendinopathy recurrence could be the absence of clearly defined and evidence-based return to play criteria. Indeed, a too early return to playing sport could deprive the injured tendon of the opportunity to adapt to conditions faced in training or competition. Consequently, assessing treatment effectiveness on the basis of precise criteria seems logical. Currently, there is a lack of consensus regarding these criteria and research needs to be undertaken to clarify this point.

Diagnosis

Generally, the reason a patient seeks medical treatment is due to pain or functional limitations. The diagnosis of tendinopathy is primarily clinical. The differential diagnosis for tendinopathy is listed in the online supplementary material 2.

Tendinopathies are clinically characterized by a gradual onset of stiffness in the tendon, activity-related pain, decreased function, and sometimes localized swelling and palpable crepitations (Andres and Murrell, 2008; Fredberg and Stengaard-Pedersen, 2008). Usually, clinical examination reveals pain with the following 3 tests: stretching, isometric contractions and palpation of the pathological area.

Although usually not required, diagnostic imaging may assist in diagnosing tendinopathy and choosing an appropriate treatment regimen. However, due to the poor correlation between diagnostic imaging and symptoms, the role of serial diagnostic imaging is limited (Khan et al., 2003).

Several imaging modalities can be used to evaluate tendinopathy. For instance, US (with color Doppler) and MRI are considered superior to conventional radiography or CT-scanners; they are usually prescribed when tendinopathy is unresponsive to treatment and entails lingering symptoms (Khan et al., 2003; Fredberg and Stengaard-Pedersen, 2008). However US, which is interactive, and certainly very operator-dependent, provides excellent morphological detail of tendons. It is also relatively inexpensive and has several significant advantages over MRI in showing the fine internal structure of tendons (showing neovascularization, thickening of the tendon, discontinuity of fibres, focal hypoechoic intratendinous areas…) (Fredberg and Stengaard-Pedersen, 2008). The extreme sensitivity of MRI means that structural abnormalities detected by imaging may not correlate

precisely with symptoms (Khan et al., 2003). A careful clinical correlation with imaging findings is therefore needed (Cook et al., 2001; Khan et al., 2003). For example, in one study, the sensitivity and specificity of US for patellar tendinopathy were calculated to be 58% and 94% respectively; for MRI, sensitivity and specificity were 78% and 86%, respectively (Warden and Brukner, 2003). Even if imaging adds little information of use for expert sports medicine clinicians in diagnosing tendinopathy, it may be useful in decision-making regarding surgical treatment or for inexperienced clinicians who are unsure of their diagnoses or unfamiliar with grading schemes (Khan et al., 2003). It is generally acknowledged that imaging shows poor predictive value in terms of development of symptoms and clinical findings (Khan et al., 2000). A recent theory explains that severe tendinopathies can be asymptomatic for a long period before the appearance of symptoms (Cook et al., 2001). Thus, chronic tendinopathies can be compared with an iceberg where pain represents the tip. It has also been suggested that through US examination of the Achilles tendons of asymptomatic athletes, it would be possible to predict a group with a risk of developing symptoms; the use of the technique thus would reduce the risk of developing chronic tendinopathies or tendon ruptures (Fredberg et al., 2008). Further studies are needed to confirm these studies and to investigate which prophylactic treatments might reduce the risk of tendinopathy occurrence (Fredberg et al., 2008).

On the other hand, no study has confirmed that radiological monitoring of patient progress has a clinical or cost benefit (Khan et al., 2003). Moreover, tendon imaging abnormalities persist even when patients have made a good functional recovery. For example, US images have been shown to remain both qualitatively and quantitatively abnormal 12 months after patellar tendon surgery, even in athletes who have returned pain-free to full competition. In terms of MRI, tendon appearance does not return to normal after successful surgery, and thus this imaging technique is not able to distinguish patients whose surgical outcome was good from those whose outcome was bad (Warden and Brukner, 2003). Consequently, imaging does not appear to have a major role to play in monitoring outcomes following surgical intervention for tendinopathy (Khan et al., 2003; Warden and Brukner, 2003).

In conclusion, clinical assessment remains the cornerstone of appropriate diagnosis and management of tendinopathy (Cook et al., 2001). US and/or MRI could be useful for confirming the diagnosis where there is some doubt, but these imaging techniques are not recommended for monitoring treatment (Khan et al., 2000).

Epidemiology

Because of differences in national sports cultures and sports habits, it is very difficult to undertake a general epidemiologic study on tendinopathies. Thus, national epidemiological studies are important in each country in order to plan prevention programmes for sports injuries.

With respect to physical workers, the prevalence of self-reported musculoskeletal symptoms has been shown to be high for the lower back (56%), wrist/hands/fingers (40%), knees (39%), and shoulders (17-36%) (Forde et al., 2005). The most commonly diagnosed musculoskeletal disorders were tendinopathies (19%) and ruptured disks in the back (18%), shoulder bursopathies (15%), and carpal tunnel syndrome (12%) (Forde et al., 2005). Common upper extremity tendinopathies include rotator cuff injury, lateral and medial epicondylitis and De Quervain's tenosynovitis (Werner et al., 2005). The incidence of shoulder tendinopathies in physical workers is estimated at 15 to 20% and ranges from 4 to 56% for hand and wrist tendinopathies (Werner et al., 2005). The risk is increased when there is a combination of high force, repetition, or exposure to vibration during repetitive work (Werner et al., 2005).

The online supplementary material 2 shows differential diagnosis and proposed risk factors for tendinopathy for each joint. We have limited ourselves to the tendinopathies of the upper and lower limbs because tendon pathologies of the trunk are definitely more difficult to isolate from other local pathologies (e.g. athletic groin pain) (Tibor and Sekiya, 2008).

a. Upper limb tendinopathies

Lateral epicondylitis (tennis elbow) is common in athletes of all ages participating in sports involving overhead or repetitive arm actions (Hume et al., 2006). Its incidence in tennis players is as high as 9 to 40% (Maffulli et al., 2003; Scott and Ashe, 2006). It is 2 to 3.5 times more frequent in people over the age of 40, in particular if playing tennis more than 2 hours per day. The

condition affects approximately 1 to 3% of the general population. The extensor carpi radialis brevis is the most frequently involved tendon but some patients also have involvement of the extensor digitorum communis (Scott and Ashe, 2006). In tennis, lateral epicondylitis is 5 to 10 times more common than medial epicondylitis (golfer's elbow) (Maffulli et al., 2003; Hume et al., 2006; Scott and Ashe, 2006). In the case of golfer's elbow, which is a typical complaint in javelin throwing, baseball and golf, coexistence of ulnar nerve pathology can be expected in up to 50% of cases with anterior subluxation of the ulnar nerve with elbow flexion (in 10 to 15% of cases), and may exaggerate or even mimic the symptoms of golfer's elbow (Maffulli et al., 2003; Scott and Ashe, 2006).

One potential cause of rotator cuff tendinopathy is shoulder impingement. This condition represents 18% of overuse injuries in adult athletes and, if untreated, may result in rotator cuff rupture (Maffulli et al., 2003). The supraspinatus is the most commonly injured muscle and Bigliani types II or III acromion are associated with increased incidence of rotator cuff tears (Scott and Ashe, 2006). Such complaints of the anterior shoulder are often present in swimmers. Anterior shoulder pain due to rotator cuff tendinopathy is often present in swimmers (until 71% of elite swimmers) (Scott and Ashe, 2006). Other throwing sports such as javelin, baseball, tennis, volleyball, or American football may also be associated with anterior shoulder pain (Kaplan et al., 2005). The shoulder is the most common site of pain reported in the wheelchair population (from 31 to 73%). Bicipital tendinopathy has also been cited as the most commonly occurring pathology in this population (Finley and Rodgers, 2004). The incidence of biceps pathology is directly proportional to the extent of rotator cuff disease (41%) and may be the result of a combination of a primary change from the impingement process and a secondary change after loss of overlying coverage by the rotator cuff (Chen et al., 2005).

De Quervain's disease, caused by stenosing tenosynovitis of the first dorsal compartment of the wrist (abductor pollicis longus and extensor pollicis brevis), is probably the best known form of paratendinopathy of the wrist and hand and is approximately six times more common in women than in men (Maffulli et al., 2003). Patients with this condition usually report pain at the dorsoradial aspect of the wrist, with referral of pain toward the thumb and/or the lateral forearm.

People may develop De Quervain's tenosynivitis following excessive use of the wrist or thumb (e.g. skiing, wringing out wet clothes, hammering, lifting heavy objects…). This condition remains the third most reported tendinopathy of the upper extremity in physical workers and it is promoted by diabetes or rheumatoid arthritis (Werner et al., 2005).

b. Lower limb tendinopathies

Achilles tendinopathy is the most prevalent lower extremity tendinopathy, with a 5.9% frequency in sedentary people and around a 50% frequency in elite endurance athletes (Scott and Ashe, 2006; Fredberg and Stengaard-Pedersen, 2008). Most common clinical Achilles disorders are mid-portion tendinopathies (55-65%), followed by insertional problems (insertional tendinopathy and retrocalcaneal bursitis; 20-25%) (Jarvinen et al., 2005). Eleven percents of soccer players report having an Achilles tendinopathy but middle- and long-distance running, track and field (7-9% of top-level runners), orienteering and jumping (volleyball, basketball, badminton) are the main sports practised by patients with Achilles tendon injury (53%), emphasizing the aetiological role of running and jumping (Maffulli et al., 2003; Jarvinen et al., 2005). Men have a higher prevalence of Achilles tendinopathy than women do before menopause (Scott and Ashe, 2006), probably due to a greater level of exercise. One study showed that forty-one percent of patients who had had an Achilles tendinopathy developed symptoms in the contralateral leg during an 8-year follow-up (Jarvinen et al., 2005). The natural history of Achilles tendinopathy remains unclear: around 30% of Achilles tendinopathies, which are resistant to conservative management undergo operative management (Paavola et al., 2000; Maffulli et al., 2003).

About one third of sports injuries treated in sports clinics concern the knees and one quarter of athletes treated for a knee injury are diagnosed with tendinopathy (Maffulli et al., 2003). The highest incidences appear in soccer (21%), basketball (13.6%), long-distance running (13%), volleyball (12%), orienteering (8%) and ice hockey (7%). The most common knee disorder is jumper’s knee, and its incidence is reported to be in the range of 7 – 40% (Scott and Ashe, 2006; Fredberg and Stengaard-Pedersen, 2008). Patellar tendinopathies represent two thirds of all pathologies of the knee induced by volleyball or basketball practice (Scott and Ashe, 2006). Other tendon complains are ilio-tibial band friction syndrome and hamstring tenosynovitis. Ilio-tibial

band friction represents approximately 14% of overuse injuries of the knee and is associated with cyclers, long-distance runners or joggers (55%), and skiers (15%). Hamstring tenosynovitis (3% of knee problems) is present in patients active in sprinting, hurdling or jumping (50%), and soccer (22%) (Maffulli et al., 2003).

Tendinopathy of the gluteus medius tendon is the main cause of greater trochanter pain syndrome (Bard, 2009). The incidence of greater trochanteric pain is reported to be approximately 1.8 patients per 1000 per year with the prevalence being higher in women and in patients with coexisting low back pain, osteoarthritis, ilio-tibial band tenderness, and obesity (Williams and Cohen, 2009). The fact that greater trochanteric pain is more common in women is perhaps due to the specific morphology of the pelvis (Tibor and Sekiya, 2008). Great trochanteric pain seems to be increasing in younger patients.

Treatments

Choices of treatment often change in parallel with physiopathological discoveries regarding tendinopathies. On the one hand, classic treatments, based on antalgic and anti-inflammatory drugs and passive physiotherapy, are often not sufficient. On the other hand, more advanced treatments exist, which have an impact on tendon structure and can lead to lasting recovery (Table IV, Fig. 2).

a. Conventional treatments

Conventional treatments are generally employed empirically to fight pain and inflammation but they do not modify the histological structure of the tendon (Croisier et al., 2001). These treatments such as relative rest or modified activity, cold, stretching, braces, antalgic physiotherapy and correction of provoking gestures are usually initially employed in acute and in the most hyperalgic phase of tendinopathy (Alfredson, 2005; Fournier and Rappoport, 2005). In a recent study using a rat model, it was demonstrated that 2 weeks of rest was often sufficient to recover from the molecular and biomechanical effects of 2 and 4 weeks of overuse (Jelinsky et al., 2008). Such findings could represent a scientific basis for the use of rest or the removal of the cause of the tendinopathy (repeated gestures), and such an approach is rational.

- ***Anti-inflammatory drugs:***

The goal of non-steroidal anti-inflammatory drugs (NSAIDs) is to reduce inflammation through the inhibition of the synthesis of inflammatory factors (inflammatory cells, prostaglandins, interleukins…) and their use has been popular for many years in the management of tendinopathy (Glaser et al., 2008). Evidence cited in the literature suggests that both oral and local NSAIDs are a reasonable option for the control of acute pain associated with tendon overuse but that they are not effective long term (Alfredson, 2005; Magra and Maffulli, 2006; Hennessy et al., 2007; Andres and Murrell, 2008; Glaser et al., 2008). In addition, long-term use of NSAIDs, even of COX-2 selective, increases the risk of gastrointestinal, cardiovascular and renal side effects associated with these medications . Although NSAIDs appear to be effective for pain control, this analgesic effect could lead patients to ignore early symptoms, entailing further damage on the affected tendon and delaying definitive healing (Magra and Maffulli, 2006). On the other hand, studies on acute tendon injuries in a rat model showed that NSAID administration did not prevent collagen degradation or loss of tensile force in tendons (Hennessy et al., 2007). However, the role of NSAIDs is still being discussed with regard to the controversy relating to inflammation in tendinopathies (Magra and Maffulli, 2006; Rees et al., 2006; Hennessy et al., 2007; Fredberg and Stengaard-Pedersen, 2008). Indeed, animal and human studies support both the overload theory and the notion that inflammation may play a role in the aetiology of acute tendinopathy. However, a degenerative process soon supersedes this (Rees et al., 2006). Moreover, it has recently been shown that an inflammatory process may be related to the development of chronic tendinopathies (Rees et al., 2006; Fredberg and Stengaard-Pedersen, 2008).

- ***Classical physiotherapy:***

There is controversy in the literature and little evidence to support the use of conservative treatments such as ultrasound (US), iontophoresis with NSAIDs, deep transverse friction massage (DTFM), or acupuncture (Brosseau et al., 2002; Green et al., 2005; Andres and Murrell, 2008). While frequently proposed in clinical settings, these modalities are reported to be effective, but only one (methodological limitations) scientific clinical study has confirmed their effects (Alfredson, 2005). However, in some studies these treatments show positive effects in the reduction of pain or in improvement in the function of patients with tendinopathies (e.g. lateral epicondylitis)

(Fournier and Rappoport, 2005; Rees et al., 2006; Hennessy et al., 2007; Andres and Murrell, 2008). Further research is required to verify whether these modalities should remain a part of tendinopathy treatment.

- ***Orthotic devices:***

Different sorts of orthotic devices exist but it is difficult to accurately assess their effectiveness in tendinopathy. Orthotics can be useful by modifying the vector strength transmitted on osseous insertion, by reinforcing proprioceptive stimulus or by correcting a static disorder (Fournier and Rappoport, 2005).

Orthotics are widely used in conservative management of tendinopathy but there is little evidence to support their effectiveness (Hennessy et al., 2007). A Cochrane review on the use of orthotic devices for epicondylitis failed to demonstrate their effectiveness (Struijs et al., 2002).

- ***Corticosteroid injections:***

At the cellular level, the anti-inflammatory and immunosuppressive activities of corticosteroids are currently considered to be attributable to the inhibition of the synthesis of cytokine genes and proinflammatory factors. In addition, the repression of genes encoding cell surface receptors and adhesion molecules in the activation, migration, and recruitment of lymphocytes mediates the anti-inflammatory effect of corticosteroids (Paavola et al., 2002).

In tendinopathy, changes in the composition of the tendinous matrix are in part mediated by inflammatory mediators and metalloproteinase enzymes and are consistent with changes in cell-mediated matrix remodelling, which precedes the onset of clinical symptoms. Corticosteroids could mediate their own effect thorough alterations in the release of these harmful chemicals agents, the behaviour of their receptors, or both (Fredberg and Stengaard-Pedersen, 2008). CSIs aim to achieve a reduction in inflammation, neo-vascularization and tendon thickness but there are also other unknown effects such as the general inhibition of protein synthesis (Fredberg et al., 2004). For these reasons, corticosteroid injections (CSIs) are commonly and successfully used to control painful tendinopathies in many common conditions (Fredberg et al., 2004; Hennessy et al., 2007; Andres and Murrell, 2008) where there is the risk of tendon rupture (Hennessy et al., 2007). Moreover, it seems that the claimed good clinical effects of local corticosteroid injections could be

mediated, at least partially, through their effect on the connective tissues and adhesions between the tendon and peritendinous tissue. This would inhibit synthesis of collagen and other extracellular matrix molecules as well as the forming of granulation tissue in these sites (Paavola et al., 2002). Although CSIs are commonly used to treat tendinopathy, there is a lack of controlled clinical series defining the exact indications for and determining the effects of such injections. Subsequently, many recommendations for using local injections of corticosteroid are not based on scientific evidence (Paavola et al., 2002). Indeed, many studies have noted an early significant improvement after a steroid injection in the short term, up to 6 weeks, but recurrences are common and in the long term (beyond 6 months) a "wait-and-see" policy or NSAID therapy can have the same results (Andres and Murrell, 2008). Thus in good practice medicine, the steroid injection would be made only to decrease pain in order to get through this hyperalgic phase in order to start physiotherapy and/or eccentric training (Stanish et al., 1986; Andres and Murrell, 2008) as soon as possible.

To summarize, there are a wide variety of conventional treatments for the management of tendinopathy, both pharmacological and non-pharmacological. These treatments have, beyond a doubt, a therapeutic interest and a relative efficacy. This efficacy would appear to be more important in the acute phase of tendinopathy, and regularly as adjuvant treatment with other techniques. However, these treatments are not completely satisfactory and the recurrence of symptoms is common. Moreover, there is little evidence to support the use of these treatments, and more controlled trials are needed.

b. **Eccentric training**

A few decades ago, Stanish (Stanish et al., 1986) was one of the pioneers of progressive eccentric exercise therapy (EET) in chronic tendinopathies, especially in Achilles tendinopathies (Alfredson, 2005; Glaser et al., 2008). More recently, eccentric programmes have been developed for the management of patellar tendinopathies (Stanish et al., 1986; Peers and Lysens, 2005; Visnes and Bahr, 2007) and lateral epicondylitis (Stasinopoulos et al., 2005; Croisier et al., 2007). Specific modalities of eccentric intervention are slow speed, low intensity and gradual intensification. Such

active treatment induces a progressive action on the tendon structure, which can lead, after a certain length of time (minimum 20 to 30 sessions of exercises), to the healing of tendinopathies, but it can also prevent relapse and chronicity (Croisier et al., 2001; Khan and Scott, 2009). However, this treatment should be painful at the beginning.

"Mechanotransduction" initiated by EET refers to the process by which the body converts mechanical loading into cellular responses which, in turn, promote structural changes (Khan and Scott, 2009). Thus, the process enhances collagen fibril alignment with increased tensile strength, encourages fibroblast activity and collagen cross-linkage formation, and prevents adhesions between the healing tendon and adjacent tissue (Stasinopoulos et al., 2005; Barone et al., 2008). Recently, it has been shown that endurance and resistance training induces tendon tissue remodelling (increase in collagen fibre content and reduction in the number of cell nuclei), which depends on the length and the intensity of workload rather than on training type (running or climbing) (Barone et al., 2008). It has also been proposed that positive effects of EET may be attributable either to the effect of stretching, with a lengthening of the muscle-tendon unit and consequently less strain experienced during joint motion, or to the effects of loading within the muscle-tendon unit, with hypertrophy and increased tensile strength in the tendon (Stasinopoulos et al., 2005; Allison and Purdam, 2009). Some theories propose that during EET, the blood flow is either stopped in the area of damage, which leads to neovascularization and improves blood flow as well as causing healing in the long term (Boesen et al., 2006), or have found that EET reduces paratendinous capilliary blood flow, consistent with a decrease in pain (Rees et al., 2008). Recently, a new theory has suggested that high-frequency oscillations in tendon force occur during EET by increased force fluctuations, rather than by force magnitude (featuring less in concentric exercises), providing the mechanism to explain the therapeutic benefit of eccentric loading (Rees et al., 2008).

Several studies have demonstrated that treatment leads to good clinical results both with (Croisier et al., 2001; Croisier et al., 2007; Frohm et al., 2007a; Frohm et al., 2007b) or without the use of a heavy load (Stanish et al., 1986; Norregaard et al., 2007). EET has superior short-term results compared to concentric training (Mafi et al., 2001). Some authors have demonstrated better results

with EET on corporeal tendinopathies in comparison with enthesopathies (Andres and Murrell, 2008; Glaser et al., 2008). New research has shown that good clinical results can be expected without loading in dorsiflexion to avoid impingement between tendon, bursa and bone in the case of Achilles tendinopathy (Jonsson et al., 2008). Other studies in the short term showed greater clinical gains, better results in terms of pain reduction and a better return to function after using a decline protocol compared with a step protocol and produced (Visnes and Bahr, 2007). Patients are also recommended to take 4 to 10 weeks of rest from sport for optimal reduction of tendinosis symptoms (Visnes and Bahr, 2007).

The benefits of isokinetic devices are well known, particularly for delivering eccentric exercises. These devices have also proven to be advantageous for the management of tendinopathies, in comparison with manual strengthening or isotonic exercises (Croisier et al., 2001; Croisier et al., 2008). The risk of worsening a tendinopathy with eccentric overload training under these controlled circumstances seems to be reduced with the use of isokinetic dynamometer (Croisier et al., 2001; Frohm et al., 2007b).

As a result, EET has become the treatment of choice for chronic tendinopathy (Achilles, patellar and epicondylitis) (Hennessy et al., 2007; Glaser et al., 2008; Allison and Purdam, 2009) even though in real life, and despite appropriate compliance, only about 60% of the patients benefit from EET (Sayana and Maffulli, 2007). Combining EET and stretching could perhaps improve results in decreasing pain; indeed, stretching seems to have similar effects to EET at 1-year follow-up in the case of Achilles tendinopathy (Norregaard et al., 2007). It has also been suggested that, in combination with EET, rehabilitation should incorporate sports-specific stretch shortening cycle and strengthening programmes (Allison and Purdam, 2009).

In summary, EET is currently considered to be the most efficient treatment for tendinopathy, even though some studies are contradictory. Nevertheless, in order to be effective, this treatment needs specific modalities: slow speed, low intensity and gradual intensification, with minimum 20 to 30 sessions of exercises often being needed.

c. More recent advances in treatment

- ***Extra-corporeal shock wave therapy:***

Over the last ten years, many clinical trials have evaluated the use of extra-corporeal shock waves therapy (ESWT) for treating patients with chronic tendinopathies. Multiple variables are associated with this therapy, such as type of shock wave generator (electrohydraulic, electromagnetic or piezoelectric), type of wave (radial or focal), intensity (total energy per shock wave/per session), frequency of the shock waves, and the protocol of application and repetitions (number of shocks) (Rompe and Maffulli, 2007). This makes the comparison of trials difficult and ESWT thus remains a controversial form of treatment. However, some studies have shown that ESWT is as effective as surgery, but cheaper, and this treatment appears to be a supplement for the treatment of those tendinopathies that are refractory to conventional therapies (Rasmussen et al., 2008). The only common factor is that, in most studies, it is necessary for the patient to experience pain during treatment, and local anaesthesia may therefore decrease the effectiveness of the treatment (Furia, 2006). Studies using high-energy ESWT have better results in tendinopathy than those using low-energy ESWT (Furia, 2006).

As explained above, in the case of tendinopathy, the damaged tendon contains disrupted and thinner collagen fibres, and there are changes in cellularity and an increase in apoptosis. The aim of ESWT seems to be to stimulate cell activity and increase blood flow, but the mechanism for this is not very clear or well understood. Possible stimulatory effects on neovascularization and inhibition of nociception with liberation of pain inhibiting substances (endorphins) are expected to occur (Mouzopoulos et al., 2007). An increase in the permeability of neuron cell membranes and cellular damage could create immediate analgesia (Andres and Murrell, 2008). Other biological effects, through the induction of specific growth factors (TGF-β1 and IGF-1) playing an important mitogenic and anabolic role, increased blood flow, inflammatory-mediated process and liberation of hydroxyproline and increased tenocyte proliferation and collagen synthesis, could induce a long term beneficial effect (6 to 8 weeks) (Chao et al., 2008). Histological observations have demonstrated that ESWT resolves oedema, swelling and inflammatory cell infiltration in injured tendons (Chao et al., 2008). The mechanisms of the therapeutic effect of ESWT on calcific tendinopathies are also uncertain. It has been proposed that increasing pressure within the

therapeutic focus causes fragmentation and cavitation effects inside amorphic calcifications and leads to disorganization and disintegration of the deposit (Mouzopoulos et al., 2007). This mechanical irritation can activate an inflammatory response and neovascularization, with leukocyte recruitment, extravasation, chemotaxis and phagocytosis (Mouzopoulos et al., 2007). There is some evidence to support the use of ESWT in calcific tendinopathies of the rotator cuff, especially with an exact focusing of the ESWT (Mouzopoulos et al., 2007) but US-guided needling in combination with ESWT seems to be more effective (Cacchio et al., 2006). The literature is not clear on the treatment of chronic tennis elbow with ESWT (Rompe and Maffulli, 2007; Andres and Murrell, 2008) but studies show that after 3 to 6 treatment at weekly intervals, with a clinical focusing, there are good results after a follow-up of more than 3 months (Rompe and Maffulli, 2007). There is no evidence supporting the use of ESWT in the treatment of medial epicondylitis (Werner et al., 2005). Studies are controversies and thus there is little evidence to justify the use of ESWT in Achilles (Furia, 2006; Hennessy et al., 2007; Glaser et al., 2008) and patellar tendinopathies (Peers and Lysens, 2005; Vulpiani et al., 2007). Recently, a case control study has demonstrated a good evolution of greater trochanteric pain syndrome after low-energy ESWT (Furia et al., 2009).

It has been demonstrated that high-energy shock waves from 0.42 to 0.54 mJ/mm² can induce tendon lesion. Thus it is recommended not to use shock waves with energy flux densities of over 0.28 mJ/mm² in the treatment of tendinopathies. Local complications reported are usually not serious: soft tissue swelling, cutaneous erosions, haematoma, local pain (Mouzopoulos et al., 2007).

Recently, a comparative study between EET and ESWT for chronic Achilles tendinopathy has shown better results with ESWT, but these findings need to be confirmed with more robust research (Hart, 2009). However, in our opinion, ESWT could be a good complementary treatment to EET for Achilles tendinopathies, as confirmed by a new article (Rompe et al., 2009). However, other series are needed to prove the real efficacy of ESWT to treat other tendinopathies.

- ***Sclerosant injections:***

These injections of 5 mg/mL polidocanol (sclerosing agent usually use to treat varicose veins) have been used to block target tendon blood flow, resulting in sclerosis in small blood vessels,

sometimes termed “neovessels”. This neovascularization, which is seen under high resolution US with color Doppler, could be associated with tendon repair (Alfredson and Ohberg, 2006) or chronic pain (Knobloch, 2008). Indeed, these “neovessels” could be associated with in-growth of nerves in areas of pathologic tendons (Rabago et al., 2009) and it is possible that theses nerve fibres are the generator of pain in chronic tendinopathies (Scott et al., 2008). These injections of polidocanol might not only sclerose the vessels, but may also eradicate the pain-generating nerve fibres (Andres and Murrell, 2008). Although polidocanol injections appear to provide pain relief, it is unclear what role they may play in tendon healing in tendinopathy (Andres and Murrell, 2008). Even though capilliary blood flow may decrease by around 25% (Knobloch et al., 2007), some authors say that there is no relationship between changes shown in US and tendon function after sclerosing treatment. Moreover, after the injection, there is initially an unexplained increased intratendinous vascularity. Some clinical series with sclerosing injections (from 2 to 7 treatments at 2-6 week intervals) report good short- and/or long-term result with an increase in strength and a decrease in pain in epicondylitis, midportion Achilles, patellar and quadriceps tendinopathies or in shoulder impingement syndrome but the same results are not found with non-sclerosing injections (Andres and Murrell, 2008; Rabago et al., 2009). Studies associating sclerosing injections and eccentric training have demonstrated a decrease in pain during eccentric training, resulting in a complete resolution of pain in the short term (Alfredson, 2005). Other studies are needed to evaluate the safety (possible sural nerve injury) and efficacy of this technique and the standardized the protocol of injection (volume, concentration) and its combination with other therapies (Rabago et al., 2009).

- ***Botulinum toxin injections:***

Few articles from the 5 last years (Wong et al., 2005; Placzek et al., 2007) have considered the possibility of making botulinum toxin injections (BTA) injections in the extensor radiali carpi brevis muscle to treat epicondylitis. This treatment is based on the fact that the paralysis caused by BTA involves a reduction in tensile stress on the enthesis. It seems that other factors are important, such as the inhibition of algogene substances (i.e. glutamate, substance P) and a destruction of pre-

ganglionic sympathetic fibres, which could explain the antalgic effect of BTA injections (Wong et al., 2005; Placzek et al., 2007). Results are contradictory and, furthermore, the treatment is expensive.

- ***Injections of blood or platelet-rich plasma:***

Injections of autologous whole blood or the blood product platelet-rich plasma (PRP) have been used for tendinopathy with the aim of providing cellular and humoral mediators to induce healing in areas of degeneration. PRP is prepared from autologous whole blood, which is centrifuged to concentrate platelets in plasma (Kaux et al., 2007; Kajikawa et al., 2008; Rabago et al., 2009). There are different techniques for preparing PRP and thus different volumes of PRP are obtained and variable platelets concentrations collected (Leitner et al., 2006; Kaux et al., 2007; Kaux et al., 2009). The intention is to augment the natural healing process at the site of pain through the action of growth factors (GFs) (PDGF, IGF-1, VEGF, bFGF, TGF-β1, EGF…) to promote matrix synthesis and wound healing (Anitua et al., 2007; Kaux et al., 2007; Andres and Murrell, 2008; Rabago et al., 2009). The balance between these GFs may have important implications in the control of angiogenesis and fibrosis (Anitua et al., 2007). Moreover, locally injected PRP has been shown to enhance the contribution of circulation-derived cells to tendon healing in the early phase of the healing process (Kajikawa et al., 2008). Some studies in laboratories have shown that PRP increases the healing of tendons and ligaments and that the different GFs have a specific action during healing (Anitua et al., 2007; Kaux et al., 2007). In vitro studies confirm the efficacy of PRP injections with improvements in Achilles tendon repair and a stronger tendon in rats (Virchenko and Aspenberg, 2006). A study on athletes confirms that, where a surgically repaired Achilles tendon tears, the use of PRP may present new possibilities for enhanced healing and functional recovery (Anitua et al., 2007). There have been only a few clinical studies, in the last 3 years, regarding the use of PRP injections for elbow tendinopathies, patellar tendinopathies and rotator cuff tears, with good results, but in vitro studies are encouraging (Mishra and Pavelko, 2006; Suresh et al., 2006; Mishra et al., 2009). Protocols include restriction from taking NSAIDs 1 to 2

days before treatment and for 10 to 14 days after treatment (Kaux et al., 2007). Other controlled trials are needed and better technique standardization could improve therapeutic efficacy.

- ***Topical glyceryl trinitrate therapy:***

Recent studies have shown that oxygen free radicals, in the correct dose, can stimulate fibroblast proliferation (Murrell, 2007). More recently NO has shown its capacity to enhance tendon healing and extracellular matrix synthesis (Murrell, 2007; Andres and Murrell, 2008; Glaser et al., 2008). Thus NO enhances collagen synthesis and results in the injured tendon having better material and mechanical properties (healing tendons are stronger on a per-unit area basis than those not exposed to additional NO) (Hennessy et al., 2007; Murrell, 2007; Paoloni and Murrell, 2007). Few clinical trials have demonstrated a beneficial effect of NO on patient-determined pain, function, and loss of symptoms of Achilles tendinopathy, chronic supraspinatus tendinopathy and tennis elbow (Murrell, 2007; Paoloni and Murrell, 2007). The most commonly described side effect seen with NO treatment is headaches, which can be severe enough to cause cessation of treatment (Andres and Murrell, 2008). As it stands, more double-blind studies would be useful to standardize this treatment (dosage, modalities of treatment….). Moreover, this therapy could be a good treatment in combination with others i.e. eccentric reeducation or ESWT but proof of its efficacy in combination is needed.

- ***Injection of MMP-inhibitor***

Aprotinin is a broad spectrum serine proteinase inhibitor (including matrix metalloproteinase MMP) with a likely mechanism of inhibition of the plamin-activation pathway of MMPs (Orchard et al., 2008). Tendon integrity depends on extracellular matrix metabolism, which is regulated by proteolitic enzymes. In tendinopathies, there are changes in the expression and activity of various matrix-degrading enzyme metalloproteinases, that are consistent with increased proteolytic activity in degenerate tendons (Andres and Murrell, 2008). The possibility of inflammatory suppression may not fully inhibit MMP-based tendon degradation, while therapies directly aimed at MMPs may be more effective. Indeed, in the last 5 years, aprotinin injections have been shown to lead to good clinical improvement: in clinical series, mild-Achilles tendinopathy patients were treated more

successfully than patellar tendinopathy patients (Hennessy et al., 2007; Orchard et al., 2008) and aprotinin injections appeared superior to both corticosteroid and saline injections (Orchard et al., 2008).

The major side effect of aprotinin (bovine-derived) is anaphylaxis, which is seen particularly after repeated use of the drug.

- ***Stem-cell or gene therapy:***

In vitro research, with encouraging results, has just begun on stem-cell and gene therapy technologies for the treatment of degenerative conditions of the musculoskeletal system such as tendinopathy (Sharma and Maffulli, 2008). In theory, pluripotent stem cells can be isolated and then delivered to an area of need such a degenerative tendon. Once the stem cells are in the desired location, either local signalling or the addition of exogenous factors can lead the pluripotent cells to differentiate into the needed cell line (Andres and Murrell, 2008). Animal studies suggest that gene therapy together with adenovirus-mediated gene therapy may also improve the capacity of the injured tendon to heal (Bolt et al., 2007).

In conclusion, many interesting new treatments are now being developed to treat tendinopathy, but currently there is little evidence to support their use in clinical practice. More well-designed controlled trials are greatly needed.

In Table V, we would like to develop the therapeutically approach, based on the available data, for each type of frequently occurring tendinopathy.

Conclusion

Chronic tendinopathy is a condition that causes many patients significant pain and disability. We focus on the importance of differential diagnosis according to localization of the problem (online supplementary material 2). Although usually not required, diagnostic imaging may assist in diagnosing tendinopathy and choosing an appropriate treatment regimen. However, due to the poor correlation between diagnostic imaging and symptoms, the role of serial diagnostic imaging is limited

Currently, the aetiology of tendinopathy is still unclear. However, it seems to be multi-factorial, involving multiple intrinsic and extrinsic factors. The role of inflammation is still debated but it seems that the absence of inflammatory cells does not mean that inflammatory mediators, such as cytokines, metalloproteinases or growth factors, are not involved in tendinopathy. These can also be implicated in the pain mechanism as well as in neovascularization. Tendinopathy often becomes chronic because the exact pathogenesis remains largely unknown.

The majority of patients will have resolution of their symptoms with classical treatments, which include rest, NSAIDs, orthotic devices, passive physiotherapy or corticosteroid injections. If, however, pain persists, active treatment (eccentric reeducation) or the use of more recently developed treatments are an option. These include ESWT, sclerosant injections, topical glyceryl trinitrate therapy, and injections of MMP-inhibitor, botulinum toxin, autologous whole blood or PRP. However, there is a need for further research into these newer treatments and further clinical series would be useful. Physicians have a variety of therapeutic options available to treat tendinopathies but, in each case, there is a lack of evidence supporting their use as the gold standard treatment, except perhaps in the case of eccentric reeducation where there is more proof of efficacy. Another approach, which is too little developed in the literature, is the use of a combination of different therapies. None of the developed treatments is now sufficient to treat tendinopathy alone.

In addition, in our opinion, one of the causes (which can be corrected) of chronicity or repeated tendinopathies is the absence of consensus regarding treatment and the return to play criteria: the absence of rest, a lack of mechanotransduction (Khan and Scott, 2009) or a too early return to playing sport does not allow the injured tendon to be adapted to conditions faced in training or competition. It is also important to consider criteria to evaluate treatment efficacy. Should they be based only on pain and ability to restart physical activity or is there a new place for imaging examination (US or MRI), though we know that abnormalities persist after that patients have good functional recovery? Currently, there is a lack of discussion in the literature regarding these criteria, and further research needs to be undertaken.

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Table I: Classification systems of tendinopathy developed by Nirschl et al[9].

Pathologic stages:

Stage I: temporary irritation (chemical inflammation?)

Stage II: permanent tendinosis – less than 50% tendon cross-section

Stage III: permanent tendinosis – greater than 50% tendon cross-section

Stage IV: partial or total rupture of tendon

Phases of pain:

Phase I: mild pain after exercise activity, <24 hours

Phase II: pain after exercise activity, >48 hours, resolves with warm-up

Phase III: pain with exercise activity, does not alter activity

Phase IV: pain with exercise activity that alters activity

Phase V: pain caused by heavy activities of daily living

Phase VI: intermittent pain at rest that does not disturb sleep; pain caused by light activities of daily living

Phase VII: constant rest pain and pain that disturb sleep

998 Table II: Aetiology of tendinopathy: proposals for predisposing factors[3, 6, 9, 29-30]. RA =
999 rheumatoid arthritis; SLE = systemic lupus erythematosus; AHT = arterial hypertension;
1000 CRF chronic renal failure.

Innate general factors	Acquired general factors	Acquired local factors
- age (> 40 years) - male gender - anatomic variants - blood type O - genetic factors	- nutrition (excess of protein) - excessive force - body composition (adiposity) - new physical activities - poor technique - training errors - high body weight/adiposity - weakness - environmental conditions - running surface - hyperthermia - drugs (oral corticosteroid or contraception, fluoroquinolones, cannabis, heroin, cocaine) - infectious diseases - general diseases (RA, psoriasis, SLE, neurological conditions, hyperuricemia, AHT, CRF, diabetes, insulin resistance, hypothyroidism, arteriosclerosis, hyperparathyroidism, glycogen	- decrease in local vascular perfusion - repetitive loading - excessive loading - abnormal and unusual movements - impingement - new/old shoes and equipment

	storage disease)	

Table III: Differential diagnosis of tendinopathy depending on localization (except for traumatic, tumoral and infectious diseases).

Localization (and percentage of incidence)	Risk factors	Differential diagnosis
- Wrist and hand (4 to 56% in physical workers)	- house cleaner - physical workers - rowing - skiing - golf - tennis - joint hypermobility - rheumatoid arthritis - diabetes - hypothyroidism	- De Quervain's disease - other wrist tendinopathies - carpal tunnel syndrome - rhizarthrosis - radial styloiditis - intersection syndrome - Guyon's canal syndrome - Wartenberg's syndrome
- Elbow (9 to 40% in tennis players)	- tennis - golf - physical workers	- tennis elbow - golf elbow - C5-C6 radiculopathy (lateral) - C8-T1 radiculopathy (medial) - posterior interosseous nerve compression - radiocapitellar osteoarthritis/chondromalacia - osteochondritis dissecans capitellum - rheumatic enthesopathy

- Shoulder (15 to 20% in physical workers and athletes, from 31 to 73% in the wheelchair population)	- volleyball - baseball - javelin - swimming - tennis - American football - wheelchair population - painter - clerical work (computer)	- rotator cuff tendinopathy - frozen shoulder - omarthrosis - acromio-clavicular pathology - instability of the shoulder - labrum / SLAP lesions - C4-C5-C6 radiculopathy - nerve lesion (suprascapular, thoracic longus, axillaris nerves)
- Hip (around 0,5% around general population)	- excess weight - skiing - ice-skating - roller-skating	- gluteus medius tendinopathy - greater trochanteric bursitis - coxarthrosis - coxitis (spondylarthropathy) - ilio-tibial band tenderness - hip osteonecrosis - pubalgia - sacroiliac pathology - labral lesion - villonodular synovitis - osteochondromatosis - stress fracture of the femur or pelvis - femoroacetabular impingement

- Knee (7 to 40% in sportsmen)	- basketball - volleyball - soccer - long-distance running - orienteering - ice hockey - cycling - track and field	- patellar tendinopathy - quadriceps tendinopathy - hamstring tenosynovitis - patellofemoral pain syndrome - prepatellar bursitis - Osgood-Schlatter disease - Sinding-Larsen-Johansson Disease - meniscal lesion - plica - Hoffa’s inflammation - stress fracture of the tibia or fibula
- Ankle (5.9% in sedentary people and around 50% in endurance athletes)	- running - soccer - track and field - jumping - volleyball - badminton - orienteering	- Achilles tendinopathy - Ligament injuries - Anterior or posterior impingement - gout - retrocalcaneal bursitis - rheumatoid arthritis - rheumatic fever - sero-negative arthropathies - Sever's Disease - stress fracture of the calcaneus

Table IV: Therapeutic effects of different treatments for chronic tendinopathies

-: no efficacy; ±: little efficacy; +: good efficacy; ++: very good efficacy; +++: excellent efficacy; (?): need more trials; ?: efficacy unknown

Treatment	Efficacy on pain (short-term)	Efficacy on pain (long-term)	Effect on recidivation
Rest & ice	++	-	-
NSAIDs	++	- to ±	-
Passive physiotherapy (US, DTFM, acupuncture…)	± to +	-	-
Orthotic devices	+	±	-
Corticosteroid injections	+++	- to ±	-
Eccentric training	+	+++	++
ESWT	++	++ to +++	+ (?)
Sclerosant injections	++	++ (?)	?
BTA injections	++	+ (?)	?
Injections of blood or PRP	± to +	+++ (?)	?
Topical NO therapy	++	+++ (?)	?
Injections of MMP-inhibitor	++	++ (?)	?
Stem-cell or gene therapy	?	?	?

1010 Table V: Effective treatments for usual chronic tendinopathies

Tendinopathies	Proposed treatments
Tennis elbow	- (Orthotic) - (US) - (Corticosteroid injection) - Eccentric training - Sclerosant injection - BTA injections - Injection of blood or PRP - Topical NO therapy
Rotator cuff tendinopathy	- US (calcific tendinopathy) - (Corticosteroid injection) - ESWT (calcific tendinopathy) - Sclerosant injection - Topical NO therapy
Jumper's knee	- Eccentric training - ESWT - Sclerosing injection - Injection of blood or PRP - Injections of MMP-inhibitor
Achilles tendinopathy	- (Orthotic) - Eccentric training - ESWT - Sclerosing injections - Topical NO therapy - Injections of MMP-inhibitor

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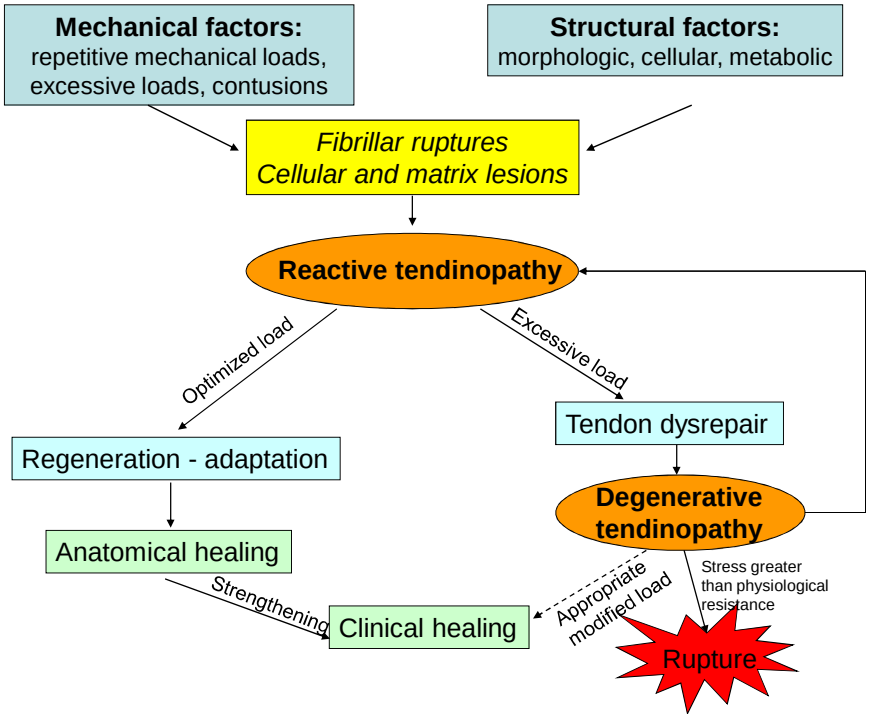
1013 Figure 1: Physiopathology of tendinopathy



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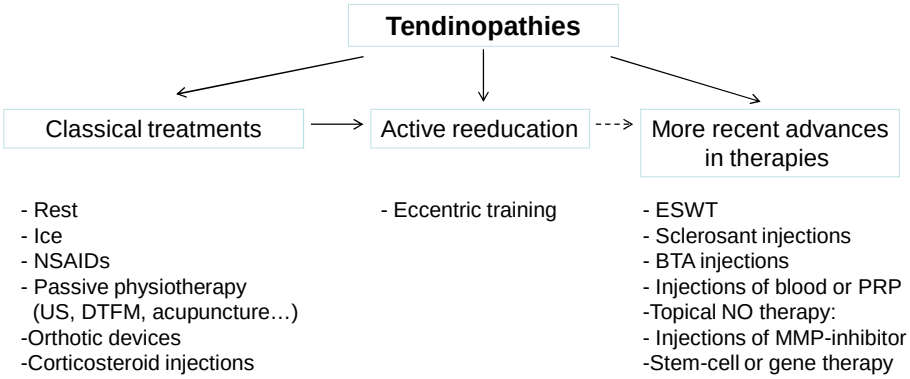
1016 Figure 2: Treatments for tendinopathies



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