Tendinopathy – update on pathophysiology

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**SYNOPSIS:** Tendinopathy has become the accepted term to describe a spectrum of changes that occur in damaged and/or diseased tendons. Over the past 2 decades there have been new insights into tendon pathophysiology of relevance to clinicians, including (1) better characterization of the overuse injury process and the resultant structural and functional disruption in chronically painful tendons; (2) improved understanding of the pathomechanics associated with chronic tendon injury; and (3) greater knowledge about the influence of lifestyle factors and drugs on tendon pathology. The implications of these new insights are discussed.

**Key Words:** collagen, medications, overuse injury, tendinitis
The current article is intended to update the reader on the science of tendinopathy pathophysiology. Over the past 2 decades we have developed a greater understanding of the process of overuse injury in tendons. In particular, we highlight recent evidence supporting the concept of “looking beyond the tendon” to address extrinsic and intrinsic factors associated with tendinopathy, including an individualized biomechanical approach. We also include a discussion of terminology used to describe tendinopathy.

“-itis”, “-osis” or “-opathy”? The challenges of terminology

In the late 1990s, Khan and co-authors advocated a shift in clinical terminology from tendinitis to tendinopathy. Both terms are typically used as generic descriptors for pain/swelling of injured tendon, without distinguishing involvement of tendon versus paratendon, or presence/absence of inflammation. Tendinopathy is an umbrella term which indicates that there is a non-rupture injury in the tendon or paratendon, which is exacerbated by mechanical loading. The term is typically used to describe the same conditions which used to be termed tendinitis. Newer evidence does indicate that inflammation accompanies, and can cause, the development of tendon overuse injury.

Terminology in relation to the description of tendinopathies has further widened since the early 1990’s, but there remain inconsistencies in the use of nomenclature. Tendinosis is a term that has been used to describe chronic midportion tendon pathology as described above, however specific definitions vary (c.f. Oxford medical dictionary 8th ed, The Oxford Dictionary of Sports Science & Medicine 3rd ed.). The term
tendinosis is used by some in preference to tendinitis to shift the focus away from inflammation. The term tenosynovitis refers specifically to pathology of a fully developed synovial sheath (eg, finger flexors/extensors), which typically presents with acute swelling with or without crepitus and triggering. Paratendonitis or peritendinitis describes involvement of the paratendon, alone or in combination with tendinosis. The clinical presentation of paratendonitis can be very similar to tendinosis (insidious onset of load-related tendon pain and thickening, with or without morning stiffness), and the 2 often co-occur.

Tendon pathomechanics

In 1992, Gross extensively summarized the current state of knowledge about tendon pathomechanics and healing. The model presented by Gross held that when tendons are chronically exposed to volumes or magnitudes of loading (tension, compression, friction) that are beyond their physiological capacity, they experience cumulative cycles of injury, inflammation, and repair leading to pain and swelling (tendinopathy). The resulting accumulation of poor-quality repair tissue in tendons is analogous to the healing after acute injury (eg, laceration or rupture), except that with overuse tendinopathy, the injury-repair response evolves gradually over time. The onset is typically insidious, and the prognosis for a patient presenting with chronic symptoms is either resolution at a frustratingly slow pace, or failure to resolve and inability to return to full activity. Without proper rehabilitation guidance to address potentially related pathomechanics, many individuals with tendinopathy are caught in a cycle of chronic
and acute-on-chronic pain as they attempt to return to activity with a poorly healed and
deconditioned tendon, and without addressing risk factors and root causes including
factors related to the kinetic chain.58

Characteristic structural changes in tendinopathic tendon

The general composition and organization of normal, healthy tendons has been well
described previously and is only briefly summarized here (FIGURE 1).42 The classic
description of the tensile load-bearing region of tendon includes 3 main components; (1)
Type I collagen fibers which are predominantly longitudinally oriented, (2) a well
hydrated, non-collagenous extracellular matrix (rich in glycosaminoglycans), and (3)
cells. The predominant cell population in healthy tendon is traditionally categorized as
collagen-producing fibroblasts, responsible for the synthesis of the collagen fibers and
extracellular matrix.42 In addition to the primary load-bearing part of the tendon, there is
an extensive network of septae (endotendon) where the nerves and vessels are mainly
located. Throughout the body, there are also structures closely associated with tendons
(bursae, sheaths, reflection pulleys, underlying joint capsules, etc). These other
structures should be assessed if possible, as they may contribute to symptoms –
particularly when they impinge on the tendon or inhibit its gliding action through the
development of adhesions.

Patients with tendinopathy display tendons that are thicker, but with reduced energy-
storing capacity, meaning that for the same load, their tendons exhibit higher strains
than those of healthy individuals(FIGURE 2).8,45 This represents a decline in both the
structural and material properties of the tendon tissue. Indeed, abnormal tendon
histology is correlated with reduced load-bearing capacity. It may be worth noting that although the stiffness (deformation in response to tensile
load) of the tissue is, on average, lower in tendinopathic tendon, this phenomenon is
unrelated to the sensation of increased “stiffness,” often mentioned by individuals with
tendinopathy, which is likely related to sensory and motor changes. These are separate
phenomena with different definitions, but which happen to have the same term in the
English language.

Prominent features of chronic tendinopathy histopathology (FIGURE 1) include the
following: a disorganization of collagen fibres, an increase in the number of vessels and
sensory nerves, an increase in the hydrated components of the extracellular
matrix, a breakdown of tissue (tendon/endotendon/paratendon) organization, and
haphazardly arranged proliferation of smaller, type III collagen fibres. There are
frequently areas of cell death (eg, hypocellularity) or alternatively of fibroblast reaction
(eg, hypercellularity and adhesions). Indeed, it is typical to find both degenerative and
reactive changes within the same biopsy, even in very severe, longstanding cases. It is
also postulated that there is a resident population of fibroblast-like cells within tendons
which, after injury, can differentiate into several lineages (osteoblast, chondrocyte,
adipocyte, tenocyte) leading to metaplasia (eg, bony, cartilaginous, or adipocyte
transformation). Metaplasia is not usually discernible on imaging (unless advanced
ossification is occurring), but is frequently encountered in biopsy specimens (reviewed
in Lui). The implication is that patients with chronic symptoms and evidence of
structural change on imaging, typically have profound underlying abnormalities which
will not be quickly resolved, and which are associated with the loss of tendon function.

At a cellular level, several authors have reported increased numbers of leukocytes
(e especially macrophages and mast cells) in chronically painful tendons (rotator cuff,
patellar and Achilles tendons),\textsuperscript{27, 56, 72, 90} as well as increased numbers of vascular cells
(endothelial and smooth muscle).\textsuperscript{93} However, compared with more immune-driven
pathologies such as rheumatoid arthritis with measurable systemic inflammation, the
number of leukocytes is small. In other words, there is indeed an inflammatory reaction
within chronically painful tendinopathy, but to a lesser extent than immune-driven
rheumatological disorders. Macrophages with accumulations of hemosiderin in their
cytoplasm are more prevalent in tendinopathic than in normal tendon;\textsuperscript{74} hemosiderin is
an indicator of prior injury indicating an activation of the innate immune response. At a
biochemical level, the cells in painful tendons produce increased levels of
glycosaminoglycan and inflammatory mediators such as substance P (SP) and
prostaglandin E2 (PGE\textsubscript{2}).\textsuperscript{34, 37, 41} SP is released by peripheral sensory nerves\textsuperscript{87} and
repetitively stretched tendon fibroblasts,\textsuperscript{11, 13} and activates local mast cells which may
contribute to pain and fibrosis.\textsuperscript{59} Tendon cells derived from tendinopathic tendon
produce more PGE\textsubscript{2} than cells from healthy individuals, indicating a chronic
upregulation.\textsuperscript{37} Taken together, the evidence suggests that during the rehabilitation
process, any worsening of edema, morning stiffness, or delayed-onset pain should be
closely monitored and controlled, as inflammation could drive the tendon further down
the pathological path. An early return to sport before adequate tendon load-bearing
capacity is a significant risk factor for recurrence of Achilles tendinopathy.\textsuperscript{39}
As a general rule, therapy should promote repair/remodelling rather than further injury/inflammation. However, it should be pointed out that there is often a discrepancy between clinical improvement, and structural improvement as measured with clinical imaging – ie, we do not yet have a good clinical outcome for tendon remodelling. At the microscopic level, as tendon heals, vessels and nerves regress, collagen fibres become stronger, and the tendon becomes less thickened, more resistant to load and less prone to reinjury, ie, recovering a more normal stress-strain curve. Longer-term ultrasound follow-up of resolved tendinopathies does indicate a reduction in tendon thickening and improved collagen alignment. This is an important point, as some authors have advocated re-injuring the tendon through treatments such as intra-tendinous needling and injections, aggressive soft tissue therapy, etc. These approaches may improve the patient’s symptoms in the short term, but could result in long-term damage to the tendon. In addition to clinical trials which show a lack of effect of this type of approach (eg, de Vos et al) the rationale is not well supported by current knowledge of pathology as outlined above.

Development of tendon pathologies due to overuse - Insights from animal models

Animal studies over the past 2 decades have demonstrated that tendons respond to overuse with a limited cellular and biochemical inflammatory response involving macrophages, mast cells, and resident fibroblasts. After 6 weeks of intensive concentric/eccentric kicking exercise, a paratendonitis with accompanying structural changes in the rabbit Achilles tendon is observed; the recruitment of inflammatory...
cells to the paratendon appears gradually over the course of 6 weeks, and
macrophages (rather than neutrophils or lymphocytes) predominate in the infiltrate. After 3 or 4 weeks of repetitive reaching and grasping, a widespread inflammatory cell
infiltrate is observed throughout overused rat forelimb and tendons— as well as a low-grade upregulation of inflammatory cytokines in the flexor tendons. This
inflammatory activity increases with more prolonged exposure to overuse. Within the
endotendon, an intrinsic inflammatory response develops in response to repetitive
tensile loading— intrinsic, because inflammatory cytokines which are known to trigger
collagen degradative activity are produced by a subpopulation of tendon cells which
reside in the endotendon. At the rabbit elbow, repetitive muscle stimulation upregulates
intrinsic inflammatory and angiogenic pathways within local tendon cells. The origin of
increased vascularity in tendinopathy may result from local vascular hyperplasia as a
result of angiogenic factors like VEGF, expressed by repetitively stressed tendon
fibroblasts.

One of the main pro-inflammatory substances involved in tendon injuries, PGE$_2$, is
produced both intrinsically (by repetitively strained tendon fibroblasts) and by
leukocytes. PGE$_2$ depresses collagen synthesis in tendon cells, and upregulates their
degradative enzyme activity. Chronic inflammation in the paratendon which is
experimentally induced (e.g. by injections of substance P or prostaglandins) causes or
exacerbates tendinopathy. Taken together, the animal studies have taught us that the
end result of overuse— tendinopathy —can develop as a result of repeated release of
inflammatory and reparative mediators.
Low-grade inflammation may come and go in short bursts following a period of intensive mechanical loading, making it difficult to detect clinically. For example, in response to repetitive loading of tenocytes, many inflammatory genes are upregulated after 4 hours, but return to baseline levels within 24 hours. However, the extent of inflammatory and fibrotic activity can also gradually increase over a period of several weeks, with prolonged exposure to repetitive loading; the tendency of inflammatory activity to increase over time is more marked in older, compared to younger, tendons.

Nevertheless, transient bursts of inflammatory activity in a tendon, if repeated and prolonged, can lead to the progressive accumulation of damage, even if these episodes are not registered as symptomatic by the patient.

The mechanism of tendinopathy pain relief in response to NSAIDs is not known, but NSAIDs are known to influence sensory nerves, tenocytes, and mast cells in addition to their well known effect on macrophages and neutrophils. The majority of animal studies which have examined the impact of NSAIDs on tendon healing (Achilles, plantaris, or flexor digitorum) after acute injury have found improved tendon healing (fewer adhesions, improved recovery of biomechanical properties), which supports the concept that ongoing tendon inflammation can be considered pathological. In contrast to the above studies of tendon injury, NSAIDs appear to be detrimental for bone-to-tendon (enthesis) healing after acute injury in rats (similar to their inhibitory effect on fracture healing) and may also be detrimental to muscle repair when used long-term. Further research is necessary to understand whether NSAIDs influence the longterm outcomes of recovery from tendinopathy.
Gross also alerted us to the fact that clinically, a single subfailure overload injury can develop into a chronic tendinopathy – this observation is supported by animal studies using partial failure models in that tendon disruption with histology very similar to that reported in humans can persist 12 months after an acute injury. Clinically, it can be very difficult to distinguish partial tears (ie, macroscopic partial defect of acute onset and marked functional deficit) from tendinopathies (which typically demonstrate a more insidious onset of pain and loss of function). Histologically, partial tears and tendinopathies have the same appearance but the extent of tissue affected in a partial tear may necessitate a different approach to finding the optimal load to allow healing and remodelling (e.g. extensive partial Achilles ruptures may benefit from a period of immobilization to prevent disruption of the healing area, much as one would protect a conservatively managed complete Achilles rupture).

**Mechanisms of injury**

The mechanism of injury for a given tendinopathy can vary from region to region, and from patient to patient. Tendons and their insertions are rarely loaded purely in tension; although tensile overload may be the dominant mechanism for many tendinopathies, there is often compression of the tendon as well, either internally (eg, one fascicle or bundle of fibres against another) or against external structures (paratendon, retinacula, bone). The combination of tension and compression results in shearing and friction. For example, the rotator cuff may experience substantial shearing forces when coming in contact with the acromion and subacromial bursa, particularly if the tendon and/or bursa
are thickened, or against the glenoid labrum in positions of extreme external rotation. The common extensor tendons of the elbow may be injured not only by repetitive tensile loading, but by shearing forces against the capitellum with rotation. In the Achilles region, shearing and torsional forces could result from the differential displacement of gastrocnemius and soleus tendon components, the "whipping/wringing" effect of excessive pronation, or friction against the adjacent plantaris tendon.

Another aspect of pathomechanics which may be clinically relevant is that of tendon stress shielding, as well as de-adaptation ("use it or lose it"). “Stress shielding” refers to the existence of a zone within a tissue which receives less load compared to surrounding areas due to microinjury of collagen fibres, or due to the uneven distribution of forces (eg, it has been proposed that there may be differential force distribution through the patellar tendon). Reduction of load through tendons (eg, bed-rest or relative inactivity) can lead to a large and rapid loss of structural organization and mechanical properties. Thus, a period of relative inactivity followed by a sudden increase in loading may precipitate a tendon injury.

Once symptoms and pain develop, ensuing movement dysfunction may contribute to the chronicity of symptoms. Tendon pain causes widespread motor inhibition in the affected region, evidenced by decreased muscular activity as assessed with electromyography. Individuals with tendinopathy also tend to use movement patterns that place excessive or abnormal load on their tendons – the faulty movement may represent either a root cause, or a reason for chronicity or slow resolution. For example, the results of several studies focusing on the relationship between jump biomechanics and patellar tendinopathy suggest that individuals with patellar tendinopathy have a less
upright position (more hip and knee flexion) at initial contact in landing. In individuals
with rotator cuff tendinopathy or tear, scapular dyskinesia is a common finding. More
prospective studies are needed, but normalizing movement patterns with the goal of
optimizing the loading environment of the tendon seems a reasonable approach.

Classification of tendinopathies according to relevant pathophysiological
features

The pathophysiology features described above lead to the following classification and
staging system for tendinopathy (TABLE 1). The classification is meant to alert
clinicians to the fact that not all tendinopathies are the same and to facilitate clinical
reasoning and communication. This system has not been extensively validated (Level V
evidence), but is rooted in the research evidence presented above and we hope that
readers will find it clinically useful.

As an example of how this classification system might be helpful in considering different
treatment options, compare and contrast the implications of a case labelled as “chronic,
grade 3, insertional Achilles tendinopathy with underlying Type II diabetes mellitus”, with
an “acute, grade 1, Achilles midportion tendinopathy with paratendinitis and increased
pronation during weight bearing.” Therapy in the first clinical scenario will need to
proceed cautiously and patiently with an exercise-based approach to stimulate
adaptation and repair, perhaps in combination with techniques to off-load the tendon
insertion (eg, heel lifts), and perhaps avoiding positions of extreme dorsiflexion which
could further exacerbate the injured enthesis. In the second clinical scenario, the
individual may be able to return to full activity rapidly if the biomechanical fault can be
adequately addressed with a trial of taping, followed by the potential use of orthoses and strengthening of the intrinsic foot musculature. Each patient can present with a unique cluster of features which preclude the use of a “recipe book” approach to physical therapy management. Based on clinical experience and knowledge of underlying pathophysiology, certain features may require more caution (eg, diabetes, advanced age), a different type of load management (eg, relative rest for more acute presentation, heavy controlled loading for more chronic presentation), balancing of rehabilitation loading with sport or work requirements, and biomechanical considerations (eg, off-loading insertion and addressing individual impairments of strength, range of motion, or motor control).

Extrinsic and intrinsic factors associated with tendinopathy

Jósza and Kannus’ classic 1997 text summarizes a number of clinical features which place tendons at risk of overuse injury. Each patient can present with a unique cluster of risk factors which may be relevant, and it is for the clinician to decide which to emphasize in assessment and treatment. Extrinsic factors include: excessive volume, magnitude, or speed of loading; training errors such as poor equipment and abrupt or acute changes in amount or type of load (eg, sudden change to a different shoe type); environmental conditions such as temperature (eg, cold weather, which makes the tendon stiffer and reduces its circulation) and ground conditions. Intrinsic factors include: individual biomechanics (malalignments, muscle weakness or imbalance, decreased flexibility), age, and adiposity. Some of these risk factors have now been observed in controlled prospective or retrospective studies.

For example, at the highest level of activity, tendinopathy is nearly universally prevalent
in some sports (eg, radiologically diagnosed rotator cuff tendinopathy in elite swimmers). Rehabilitation programs emphasizing individualized biomechanics and overall movement/function have recently been validated in large randomized controlled trials, underlining the potential importance of biomechanics in the etiology of tendinopathy.

With regards to adiposity as a risk factor for tendinopathy, an association between elevated body mass index and increased risk of tendinopathy appears to hold true both for lower extremity tendons (Achilles, patellar) and upper extremity tendons (rotator cuff, elbow). The biological mechanisms have not yet been established, but excessive dietary intake of cholesterol does result in the accumulation of oxidized low density lipoprotein in the load-bearing region of tendon, where it impairs Type I collagen production and reduces tendon strength and energy storage capacity. Individuals with tendinopathy who have a body mass index or waist girth above healthy reference values could be informed that their diet or their weight may be contributing to their tendon condition, and an appropriate exercise prescription made (and perhaps a lipid profile should be suggested if it has not been done recently). Generalized exercise targeted at weight loss, e.g., for the overweight individual with rotator cuff tendinopathy or golfer’s elbow, may also address concomitant features of chronic musculoskeletal pain syndromes, such as decreased pain threshold and emotional depression.

Smoking is also associated with worse tendon histology than that seen in non-smokers.

**Medications**
In the following section, we provide an update on the role certain medications are now known to play in causing or exacerbating tendinopathy.\(^5\) A complete history of any patient will always include their medications, but patients with tendinopathy should specifically be asked about the medications listed below. Tendon pathology caused by medications may present similarly to an overuse condition (eg, gradual onset, and pain and swelling aggravated by activity; features typical of statin-induced tendinopathy), or the onset may be sudden, at times characterized by a spontaneous rupture (as characteristic of many fluoroquinolone-induced tendinopathies).

Statins

Statin-induced tendinopathy was first reported in the 2000s.\(^5\) The predominant musculoskeletal complaint with this class of drugs is myalgia, but tendinopathy (in the form of tendinosis and tenosynovitis) is also a side-effect. The incidence of statin-induced tendinopathy is not known, but it is thought to be rare, accounting for approximately 2\% of all complications in one study.\(^6\) As with fluoroquinolones, the main location is the Achilles tendon, and other reported sites are the rotator cuff and lateral elbow. The median time of onset is 10 months, and about 1 third of cases result in frank rupture.\(^5\)

Fluoroquinolones

Fluoroquinolones are a class of synthetic anti-microbial drugs, including commonly used medications such as ciprofloxacin and levofloxacin. The fact that tendinopathy can occur as a side effect of these drugs was not widely recognized until the early 2000s.\(^5\) The estimated rate of tendinopathy in response to fluoroquinolone treatment is 0.5 –
2.0%, with the Achilles tendon being the most commonly affected (about 90% of cases, of which about half are bilateral). Other reported sites include the rotator cuff, lateral elbow, finger and thumb flexors, and quadriceps tendon. The onset is usually acute (median duration 8 days after beginning treatment). Approximately 40% of cases affecting the Achilles tendon proceed to frank rupture. Those at greatest risk of fluoroquinolone-induced tendinopathy are people over 60 years of age, people receiving concomitant corticosteroid therapy, those with renal problems, or patients with pre-existing tendinopathy.

Corticosteroids

Corticosteroids can impair local collagen synthesis, resulting in tendon atrophy, reduction of tensile strength, and hence decreased load to failure. The potential for complete tendon rupture with loading after steroid injection is recognised although the literature is limited to case reports. Rigorous studies have not been performed. However, local steroid injections in the vicinity of the Achilles or patellar tendon and in the presence of severe tendinosis or a tear are frequently discouraged due to the concerns with respect to rupture of heavily loaded tendons and/or impairment of tissue repair where disruption is already present.

Other causative or contributing medical conditions

A number of medical conditions are associated with tendinopathies and ought to be considered relevant when conducting the history and clinical examination. These are described in Table 2. Some patients present with multiple tendon injuries, with or without a family history. Despite the fact that a number of gene variants have been
identified that are associated with increased risk of tendon injury or tendinopathy, there is no clinically useful genetic test but a positive family history or tendinopathies at multiple locations could signal an elevated risk.

Conclusion

Although tendons are anatomically designed to withstand extensive mechanical loading, they are prone to injury through a variety of biomechanical and biological mechanisms. The healing response may be slow or incomplete in many individuals, resulting in long-term structural and functional deficits that predispose to ongoing irritation and pain. However, the clinical presentation and prognosis of tendinopathy can be very individualized (acute or chronic, focal or generalized, paratendon versus tendon, etc), and a detailed assessment of the extent or nature of pathology and risk factors can assist in clinical reasoning.
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### TABLE 1. Clinical features of tendon injuries

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Classification</th>
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<tbody>
<tr>
<td><strong>Time</strong></td>
<td></td>
</tr>
<tr>
<td>Acute: &lt; 4 weeks</td>
<td></td>
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<tr>
<td>Subacute: 5-12 weeks</td>
<td></td>
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<tr>
<td>Chronic: &gt; 12 weeks</td>
<td></td>
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<tr>
<td>Acute on chronic</td>
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<tr>
<td><strong>Tissue affected (more than 1 can be affected)</strong></td>
<td>Tendon</td>
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<tr>
<td></td>
<td>Enthesis</td>
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<td></td>
<td>Paratendon</td>
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<td></td>
<td>Tenosynovial sheath</td>
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<tr>
<td><strong>Additional features</strong></td>
<td>Increased colour Doppler signal and fluid around (as opposed to within) a tendon suggesting inflammation (tenosynovitis, paratendinitis)</td>
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<td></td>
<td>Calcification (primary or dystrophic)</td>
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<td></td>
<td>Bony deformity (eg, subacromial spur, insertional irregularity suggestive of inflammatory enthesitis)</td>
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<tr>
<td></td>
<td>Bursitis (some will communicate with tendon sheath)</td>
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<tr>
<td></td>
<td>Adjacent structures (eg, underlying joint pathology)</td>
</tr>
<tr>
<td><strong>Degree of tissue disruption on cross section at any site</strong></td>
<td>Grade 1 &lt; 10%, Grade 2 10 - 50%, Grade 3 &gt; 50% cross-sectional area (eg, on transverse ultrasound or magnetic resonance imaging)</td>
</tr>
<tr>
<td><strong>Underlying (risk) factors</strong></td>
<td>Intrinsic risk factors (biomechanics, family history, sex, age)</td>
</tr>
<tr>
<td></td>
<td>Extrinsic risk factors (training errors, sport or occupational demands, etc)</td>
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<td></td>
<td>Medical conditions</td>
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### TABLE 2. Medical conditions with associated tendon pathology

<table>
<thead>
<tr>
<th>Site of tendon affected</th>
<th>Examples of medical conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid portion</td>
<td>Dyslipidemias, Rheumatoid disease, tumours, infections, storage diseases, gout, pseudogout, heritable connective tissue diseases, haemachromatosis, endocrinopathies (including thyroid disease, cushings, hypogonadism, menopause), metabolic diseases including diabetes, hypercalcaemia</td>
</tr>
<tr>
<td>Enthesis</td>
<td>Psoriasis, gout, pseudogout, spondyloarthropathies, inflammatory bowel disease</td>
</tr>
<tr>
<td>Tendon sheath</td>
<td>Rheumatoid arthritis, infections, tumours</td>
</tr>
</tbody>
</table>
FIGURE 1. Structural changes in chronic human Achilles tendinopathy. The left side of the hypothetical tendon is healthy. Collagen fibres are tightly bundled, and predominantly Type I collagen. Blood vessels are sparse, and primarily located in the looser connective tissue which surrounds the collagen bundles (blown up area). The right side represents typical changes in a tendinopathic tendon. Collagen fibres are thinner and more loosely organized, and contain a higher amount of Type III collagen. There is an increase in the amount of proteoglycans (yellow and blue), leading to increased water content (swelling) within the tissue. These structural changes are consistent with tissue injury, and can include both degenerative areas (e.g., extensive cell death or metaplasia), and reactive areas where ongoing healing or fibrosis appears.
to be occurring. Figure from Clinical Sports Medicine 3rd edition, Brukner and Khan, 2006. Reproduced with permission of McGraw Hill.
**FIGURE 2.** Functional impairment in chronic human Achilles tendinopathy. The average stress strain curve of tendinopathic Achilles tendons indicates a decline in material properties including modulus and energy storage, compared to normal tendon. Figure from Arya and Kulig 2010\(^8\) reproduced with permission of the American Physiological Society.