A ‘‘polypill’’ for acute tendon pain in athletes with tendinopathy?

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**Summary** Acute tendon pain in athletes is a condition that is difficult to manage. There are few treatment options that give adequate pain relief and have a theoretical basis for efficacy. We report the use of a novel ‘‘polypill’’ for tendon pain, and provide evidence for the basis for its use. We present it to stimulate discussion and research into a new area of tendinopathy.

**Introduction**

Athletes with tendinopathy who present with acute tendon pain are particularly problematic to manage clinically. Treatment for acute tendon pain is limited to pharmacotherapy and load management, as physical measures have little effect.

The most commonly used pharmacological agents in tendinopathy are non-steroidal anti-inflammatory drugs (NSAIDs). They were used to control the inflammation originally thought to be present in tendinopathy, but most cases of tendinopathy do not have the classical features of inflammation.\(^1\) Indeed, tendinopathy does not respond well in the short or medium term to NSAIDs,\(^2\) any effect perhaps being due to their analgesic action.

Other options for the treatment of acute tendon pain and pathology in athletes with tendinopathy are needed. However, as the source of tendon pain has not been clearly described, it is difficult to prescribe treatment that directly affects pain. We propose the consideration of complementary factors that may be implicated in the tendon pain and pathology paradigm. We also present some evidence for their mechanisms and suggest a treatment approach based on these effects.

A normal tendon has quiescent cells in a structured matrix with sufficient vascularity and minimal neural supply. There are four primary changes in tendinopathy; cellular activation or degeneration/death, increases in proteoglycans, collagen disruption and neural and vascular ingrowth. There is some evidence that the tendinopathy process is staged; the changes are cell driven, producing proteoglycan increases that result in
collagen disruption. This, over time, stimulates neovascularisation.\(^3\)

The critical change in the matrix is a modification of the major proteoglycan type in ground substance from small (decorin and biglycan) to large proteoglycans (aggrecan and versican). These larger molecules bind more water than small proteoglycans and are implicated in disrupting normally tightly packed collagen. These changes increase the fibrocartilaginous constituents of the tendon.

Load is clearly implicated in tendon pain and pathology. Load can have both a positive and negative effect on tendon, as it has been implicated in both the onset of, and recovery from, pathology and pain. The type and amount of load which leads to anabolic or catabolic effects has yet to be defined. A load induced tendinopathy is likely driven by multiple factors that have complex interactions. Tendon cells and matrix are likely affected by growth factors, cytokines and matrix metalloproteinases (MMPs) both early and later in the process.\(^4\)

The major clinical aim in tendinopathy is to reduce load-related pain, with an associated ideal of having a positive effect on tendon pathology. Some factors that are implicated in pathology can, independently or in combination, cause pain, giving them a potential role in acute pain in a pathological tendon. One factor strongly implicated in structural matrix change as well as pain is tumour necrosis factor alpha (TNF\(_\alpha\)). In addition, some NSAID treatments have been shown to affect both pain and pathology. We have experimented clinically with pharmaceutical interventions to enhance pain relief with a view to positively affecting pathology. We discuss specific treatment options below.

### Treatment of tendon pain

#### Selective NSAID prescription

Recent research and clinical experience suggests that NSAIDs may act via mechanisms other than those which alter the standard inflammatory cascade. Ibuprofen, indomethacin and naproxen have been demonstrated to inhibit aggrecan expression in in-vitro tendon preparations,\(^5\) and limiting aggrecan expression has a beneficial effect on the matrix. The use of ibuprofen in tendinopathy is supported by studies of tendon repair after transection, where ibuprofen was the only NSAID of six NSAIDs not to have a detrimental effect.\(^6\)

#### TNF\(_\alpha\) inhibitors

Tumour necrosis factor alpha is implicated in enthesopathy associated with spondyloarthropathy and tendon cells have selective binding sites for TNF\(_\alpha\).\(^7\) Some evidence exists that TNF\(_\alpha\) may affect both structural change and pain in activity-induced tendinopathy.

Tumour necrosis factor alpha expression is greater in ‘inflamed’ equine tendons when compared to normal or scarred tendons.\(^8\) Up-regulation of TNF\(_\alpha\) is also associated with apoptosis.\(^9\) Apoptosis may be a key process in tendinopathy in humans as apoptotic cell death was recently shown to be a feature of patellar tendinopathy in humans.\(^10\)

Other links between TNF\(_\alpha\) and tendinopathy are more tenuous. Increased amounts of intra-abdominal adiposity have been linked with higher serum levels of TNF\(_\alpha\), C reactive protein and interleukin-6 (IL-6).\(^11\) Greater waist girth (a measure of extra-abdominal adipose tissue) has been associated with patellar tendinopathy.\(^12\)

Inhibition of TNF\(_\alpha\) in spondyloarthropathy is obtained with receptor blockers or monoclonal antibodies, however side effects are of concern and the treatment is expensive. A similar but less potent effect may be obtained with relatively inexpensive groups of antibiotics. Doxycycline, commonly used in acne for both antibacterial and anti-inflammatory effects, has been shown to block the action of TNF\(_\alpha\).\(^13\) In addition, macrolide antibiotics, such as erythromycin and azithromycin inhibit the production of pro-inflammatory cytokines, including IL-1, IL-6, IL-8 and TNF\(_\alpha\) and have been shown to reduce inflammation associated with a number of respiratory disorders.\(^14\)

A comparison of the effects of specific TNF\(_\alpha\) blockers and antibiotics with a similar effect on one specific action of TNF has been performed in animals. Olmarker and Larsson\(^13\) investigated the effects of nucleus pulposis tissue on lumbar nerve conduction velocity and showed that the presence of TNF\(_\alpha\) in the nucleus pulposis was partly responsible for the reduction in nerve conduction velocity. A selective antibody to TNF\(_\alpha\) limited reduction in nerve conduction velocity but not significantly compared to the control group, however doxycycline effectively blocked the reduction in nerve conduction velocity.

Doxycycline also inhibits connective tissue breakdown,\(^15\) that may have additional benefits in tendinopathy. Increased collagen turnover, associated with augmented activity of MMP-1. MMP-2 and MMP-3, has been demonstrated in human cases of
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Investigation.

In recent years, there has been increasing interest in the use of "polypills" for the treatment of various conditions. A polypill is a single tablet containing multiple medications. The rationale behind this approach is that it can simplify medication regimens and potentially improve adherence to treatment. This may be particularly useful in the context of tendinopathy, a condition that frequently affects athletes and often requires a combination of medications for optimal management.

Doxycycline has been demonstrated to inhibit MMP-1 and MMP-2 in a number of animal models of inflammation and it has also been shown to reduce MMP activity in patients with gingival inflammation. Doxycycline has been shown to inhibit MMP-8 and MMP-9 activity and also the synthesis of MMPs in human endothelial cells. Doxycycline has been shown to reduce the activity of procollagenase in osteoarthritic knees and to slow the rate of progression of this disorder. A similar effect in tendon has been demonstrated and doxycycline and ilomastat have been shown to significantly inhibit pericellular matrix degeneration and loss of material properties of tendon associated with stress deprivation, through its effect on TNFα.

Ibuprofen may enhance the effect of doxycycline on tendons as similar NSAIDs (flurbiprofen) potentiate the effect of sub-microbial doses of doxycycline when used in periodontal inflammation. This effect is thought to be a class effect mediated by reduction of upregulation of MMPs mediated by prostaglandin E2. Paradoxically, most anti-inflammatory agents (naproxen celecoxib, diclofenac) increase TNFα levels. In addition, non pharmacological substances reported as having inhibitory action on TNFα actions include polyphenols and catechins contained in green tea and omega 3 fatty acid (fish oil) preparations and these may warrant further investigation.

Dosage

Standard anti-inflammatory (Ibuprofen 400 mg tds) and anti-microbial doses (Doxycycline 100 mg daily) are given to athletes with acutely painful tendinopathy. The medication is continued for 14–28 days with an impression of optimal effect by the third week. The addition of non-pharmaceutical medications such as green tea or omega 3 fatty acids can be without restriction.

Conclusion

Despite the preliminary nature of the basic science data and being cognisant of the potentially conflicting actions of some of the agents, we consider the utilisation of a poly pill approach, combining doxycycline with ibuprofen and the optional addition of a non-pharmacological agent, as a potential treatment for tendinopathy with acute pain, worthy of consideration and further assessment.

References


