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OPINION PIECE

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

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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 (TNFα). 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]

TNFα inhibitors

Tumour necrosis factor alpha is implicated in enthesopathy associated with spondyloarthropathy and tendon cells have selective binding sites for TNFα.[7] Some evidence exists that TNFα 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 TNFα 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 TNFα and tendinopathy are more tenuous. Increased amounts of intra-abdominal adiposity have been linked with higher serum levels of TNFα, C reactive protein and interleukin-6 (IL-6).[11] Greater waist girth (a measure of intra-abdominal adipose tissue) has been associated with patellar tendinopathy.[12]

Inhibition of TNFα 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 TNFα.[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 TNFα and have been shown to reduce inflammation associated with a number of respiratory disorders.[14]

A comparison of the effects of specific TNFα 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 TNFα in the nucleus pulposis was partly responsible for the reduction in nerve conduction velocity. A selective antibody to TNFα 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

tendon pathology.[16] Doxycycline has been demonstrated to inhibit MMP-1 and MMP-2 in a number of animal models of inflammation[15] and it has also been shown to reduce MMP activity in patients with gingival inflammation.[17] Doxycycline has been shown to inhibit MMP-8 and MMP-9 activity and also the synthesis of MMPs in human endothelial cells.[18] Doxycycline has been shown to reduce the activity of procollagenase in osteoarthitic knees and to slow the rate of progression of this disorder.[19] 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.[20]

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 E_2. Paradoxically, most anti-inflammatory agents (naproxen celecoxib, diclofenac) increase TNFα levels.[21,22] In addition, non pharmacological substances reported as having inhibitory action on TNFα actions include polyphenols and catechins contained in green tea[23] and omega 3 fatty acid (fish oil) preparations[24] 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

1. Khan KM, Bonar SF, Cook JL, et al. Histopathology of common overuse tendon conditions: update and implications for clinical management. *Sports Med* 1999;**6**:393—408.
2. Almekinders L, Temple J. Etiology, diagnosis, and treatment of tendonitis: an analysis of the literature. *Med Sci Sport Exer* 1998;**30**(8):1183—90.
3. Cook JL, Feller J, Bonar SF, et al. Abnormal tenocyte morphology is more prevalent than collagen disruption in asymptomatic athletes' patellar tendons: Is this the first step in the tendinosis cascade? *J Orthop Res* 2004; **24**:334—8.
4. Magra M, Maffulli N. Matrix metalloproteases: a role in overuse tendinopathies. *Br J Sports Med* 2005;**39**(11): 789—91.
5. Riley GP, Cox M, Harrall RL, et al. Inhibition of tendon cell proliferation and matrix glycosaminoglycan synthesis by non-steroidal anti-inflammatory drugs in vitro. *J Hand Surg - Br Eur Vol* 2001;**26B**(3):224—8.
6. Ferry ST, Dahners LE, Afshari HM, et al. The effects of common anti-inflammatory drugs on the healing rat patellar tendon. *Am J Sports Med* 2007;**35**:1326—33.
7. Hosaka Y, Sakamoto Y, Kirisawa R, et al. Distribution of TNF receptors and TNF receptor-associated intracellular signalling factors on equine tendinocytes in vitro. *Jpn J Vet Res* 2004;**53**:135—44.
8. Hosaka Y, Kirisawa R, Ueda H, et al. Differences in tumor necrosis factor (TNF)alpha and TNF receptor-1-mediated intracellular signaling factors in normal, inflamed and scar-formed horse tendons. *J Vet Med Sci* 2005;**67**:985—91.
9. Rath PC, Aggarwal BB. TNF-induced signalling in apoptosis. *J Clin Immunol* 1999;**19**:350—64.
10. Lian O, Scott A, Engebretsen L, et al. Excessive apoptosis in patellar tendinopathy in athletes. *Am J Sports Med* 2007;**35**(4):605—11.
11. Park HS, Park JY, Yu R. Relationship of obesity and visceral adiposity with serum concentrations of CRP, TNF-alpha and IL-6. *Diabetes Res Clin Pract* 2005;**69**(1):29—35.
12. Malliaras P, Cook JL, Kent PM. Anthropometric risk factors for patellar tendon injury among volleyball players. *Br J Sports Med* 2007;**41**(4):259—63.
13. Olmarker K, Larsson K. Tumor necrosis factor (alpha) and nucleus-pulposis-induced nerve root injury. *Spine* 1998; **23**:2538—44.
14. Rubin BK. Immunomodulatory properties of macrolides: overview and historical perspective. *Am J Med* 2004;**117**:2S—3S.
15. Golub LM, Ramamurthy NS, McNamara TF. Tetracyclines inhibit connective tissue breakdown: new therapeutic implications for an old family of drugs. *Crit Rev Oral Biol Med* 1991;**2**:297—322.
16. Riley GP, Curry V, DeGroot J, et al. Matrix metalloproteinase activities and their relationship with collagen remodelling in tendon pathology. *Matrix Biol* 2002;**21**(2): 185—95.
17. Lee H, Cianco SG, Tuter G, et al. Doxycycline and NSAID in periodontal therapy. *J Periodont* 2004;**75**:453—63.
18. Hanemaaijer R, Visser H, Koolwijk P, et al. Inhibition of MMP synthesis by doxycycline and chemically modified tetracyclines (CMTs) in human endothelial cells. *Adv Dent Res* 1998;**12**:114—8.
19. Brandt KD, Mazzuca SA, Katz BP. Effect of doxycycline on progression of osteoarthritis. *Arth Rheum* 2005; **52**:2015—25.

20. Jain A, Brennan F, Nanchahal J. Treatment of rheumatoid tenosynovitis with cytokine inhibitors. *Lancet* 2002;**360**:1565—6.
21. Nalbant S, Akmaz I, Kaplan M, et al. Does rofecoxib increase TNF-alpha levels? *Clin Exp Rheumatol* 2006;**24**:361—436.
22. Endres S, Whitaker RED, Ghorbani R, et al. Oral aspirin and ibuprofen increase cytokine-induced synthesis of IL-1 beta and tumour necrosis factor-alpha ex vivo. *Immunology* 1996;**87**:264—70.
23. Cao H, Kelly MA, Kari F, et al. Green tea increases anti-inflammatory tristetraprolin and decreases pro-inflammatory tumor necrosis factor mRNA levels in rats. *J Inflamm* 2007;**4**:1—12.
24. Mehra MR, Lavie CJ, Ventura HO, et al. Fish oils produce anti-inflammatory effects and improve body weight in severe heart failure. *J Heart Lung Transplant* 2006;**25**(7):834—8.