THROW AWAY THE ANTI-INFLAMMATORIES & START LOADING YOUR DAMAGED TENDONS

EVIDENCE INTO PRACTICE

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Tendons in our body ensure that muscle contractile force is transferred to bone and thereby enables locomotor function. When we exercise, we are exposed to high amounts of loading which tissue adapts to, some more so than others. Whereas the skeletal and heart musculature can adapt quite dramatically with training, the adaptive response of connective tissue, such as tendon, which is dominated by collagen, is more moderate. From human studies we know that collagen synthesis rises in response to loading[1], and that although this indicates that one of the building blocks for the tendon is formed, it does not guarantee any new tendon structure formation. Accordingly, it has been revealed that the core of the human Achilles tendon has almost no turnover in adult life[2], which fits with observations of horse tendons[3]. Despite this lack of evidence for any structural changes in the tendon with regular physical activity after the age of 18, tendon hypertrophy is seen in response to long-term training with exercises that load the Achilles tendon[4]. So, what could potentially happen with training is the addition of thin layers of collagen tissue on the surface of the tendon, almost like adding 'rings' to a tree as it grows older, or it may be that the tendon has a small modifiable turnover pool of collagen that in itself has no influence on the primary structure of the tendon. With loading of the tendon, the blood flow, metabolism and the peritendinous concentration of inflammatory markers like prostaglandins can be upregulated[5,6]. Along with these responses, collagen proteolytic enzyme activity and collagen degradation are also found to increase[7].

During exercise, blood flow of the tendon can increase up to 10-fold in an intensity-dependent manner[8], and when prostaglandin release is inhibited by anti-inflammatory medication, this exercise-induced rise in tendon blood flow can be reduced by approximately 30%. This effect is specific for cyclooxygenase-2 (Cox-2) mediated pathways, in accordance with this pathway being inducible by exercise. This indicates that an increase in tissue prostaglandin plays a significant role for blood flow in tendon connective tissue during physical loading in vivo. In support of a connection between tendon loading and release of inflammatory mediators, tendons from mice subjected to treadmill running showed increased concentrations of prostaglandins. In vitro studies on human fibroblasts also show a rise in production of

inflammatory mediators in a stretching magnitude-dependent pattern[9].

TENDON TISSUE FORMATION AND INFLAMMATION

It has been shown that anti-inflammatory medication was able to diminish the prostaglandin response to mechanical loading of human fibroblasts isolated either from the patellar tendon or the hand tendon stretched in vitro[10,11]. The effect of anti-inflammatory medication on the local prostaglandin level in the human patellar tendon was also lower for 3 days after exercise compared to the non-blocked tendon[12]. Also, the exercise-induced increase in tendon collagen synthesis was reduced. These findings suggest that intact activation of inflammatory pathways is important for the physiological rise in the collagen synthesis that is seen with mechanical loading of tendon tissue. The influence of anti-inflammatory medication on the training-related adaptation of human tendons has been investigated in both young and elderly individuals. No significant adaptation in the morphological tendon size was seen, whereas the normalised tendon deformation and strain decreased with training, but medication did not change this outcome of training[13]. This suggests that tendon tissue shows no substantial change in tendon content of collagen or fibrillar structures but may modify its mechanical properties through, for example, cross links, and that such changes are not diminished with the administration of anti-inflammatory medication. Interleukins have been suggested to play a role in tendon adaptation to loading. Prolonged running results in a rise in the tissue concentration of interleukin-6 (IL-6). Based on this, the exercise-induced rise in interleukins was suggested to be the 'inflammation-mediator' of mechanical stimulation of collagen synthesis. When human recombinant IL-6 was infused locally, collagen synthesis in the peritendinous tissue rose to a similar degree as with exercise[14]. This suggests that IL-6 is an important stimulator of collagen synthesis, and can act independently of any mechanical tendon loading.

INFLAMMATION, EXERCISE AND PROTEOLYSIS

Proteolytic activity of the tendon can increase in response to acute exercise. Further, in vitro studies on rabbit tendon showed that the combination of mechanical stretch and the inflammatory cytokine IL-1b synergistically increased the expression and activity of proteolytic enzymes[15]. Also, human patellar tendon fibroblasts responded to IL-1b with increased proteolytic expression[9]. This suggests that mechanical loading, together with inflammatory cytokines, can alter matrix proteolytic enzymatic activity. IL-1b and mechanical stretch can both induce COX-2 expression in tendon fibroblasts as individual treatments, and combining these two treatments can induce a more pronounced response. However, low doses of IL-1b can also repress expression of some genes induced by mechanical stretch[16]. Thus, it appears that there are some interactions between inflammatory cytokines, loading and the potential for matrix degradation. Interestingly, studies have shown that mechanical loading was necessary to protect tendon collagen bundles cultured in the presence of inflammatory cells from degradation and loss of mechanical

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integrity[17,18]. This suggests that mechanical loading is a primary mechanism for reducing susceptibility of collagen fibrils in tendon tissue to enzymatic degradation. This protective effect of tensile strain is supported by findings made in other collagen-rich connective tissues, and underlines the importance of mechanical tension for tendon homeostasis. It appears that inflammatory mediators do play a role in the adaptation of healthy human tendon tissue to mechanical loading. Thus, both inflammatory markers and collagen turnover are modulated in the peritendinous tissue with loading, and the removal of the inflammatory response to physiological tissue loading seems detrimental for the collagen response.

TENDINOPATHY AND INFLAMMATION

Tendinopathy displays characteristics of degenerative changes in the tissue but in general lacks signs of inflammatory responses[19]. Tendinopathic tendon demonstrates changes in cell shape and density, presented as a rounding of the normally elongated tendon fibroblasts and showing areas of increased cell density as well as areas with very low cell numbers. In addition, the normally well-aligned collagen fibres lose their organisation and a thickening of the tendon due to accumulation of proteoglycans, and thus water is seen[19]. In addition, a chronic up-regulation of the expression of several structural proteins, proteolytic enzymes and growth factors is observed in tendinopathy[19]. However, there is no sign of any up-regulation in the expression of inflammatory signal mediators. Somewhat in contradiction to the lack of inflammatory up-regulation in tendinopathic tendon is the demonstration – in the short-term, at least – of a clinical effect of anti-inflammatory treatment with glucocorticoids[20]. This could be because when at rest, no inflammatory signs are present, whereas during times like after heavy mechanical loading (e.g. running) an inflammatory response could potentially be present. However, in patients with chronic tendinopathy, a presence of inflammatory mediators in response to acute running was not shown, and subsequently nor was any influence of inflammatory medication[21]. This finding demonstrates that inflammatory signalling is not exaggerated in tendinopathic compared to healthy regions of the tendon after physical activity. In line with this, no convincing evidence exists for the substantial historical use of anti-inflammatory drugs in treatment of painful or overloaded tendons[22]. However, it cannot be excluded that tendinopathic conditions only demonstrate inflammatory characteristics very early in the disease. Several authors have suggested a two-phase response with an early inflammatory-dominated response followed by a later degenerative response[23], whereas others maintain the idea that tendinopathy is a degenerative phenomenon without inflammation[24]. Presently, the full explanation for development of tendinopathy remains elusive with two suggestions being currently proposed. One theory posits that tendinopathy reflects a misbalance between overloading of the tissue resulting in both a cell reaction towards apoptosis and increased proteolytic activity[25]. An alternate theory suggests a local unloading of tendon cells due to micro-ruptures of collagen fibres as an initial step in pathological changes seen in tendon injuries[26]. In this scenario, it would be the absence of tensile stimuli that would trigger catabolic alterations of tendon tissue[26].

TENDON RUPTURE AND INFLAMMATION

Rupture to the tendon and the subsequent healing is associated with inflammatory activity, and the initial inflammatory period is followed by a later period of proliferation and remodelling where inflammation is less pronounced and scar formation and fibrosis occur[27]. This supports the view that tendon healing has transient changes in the degree of inflammation present. The inflammatory phase seems to be influenced by the degree of mechanical loading during the healing process. When rat tendon was mechanically injured, inflammation-associated genes were altered both in response to a single loading episode or with more continuous loading[28]. The induced expression of inflammatory mediators during early tendon healing was lowered when tendons were loaded, and was coupled with an improved matrix synthesis and thicker, stronger tendons. This suggests a beneficial role of mechanical loading and inflammatory signalling upon tendon adaptation. Further, inhibition of inflammatory mediators during tendon healing after acute injury appears to inhibit the healing progression[29].

CONCLUSION

In conclusion, studies on healthy tendons have shown that inflammatory markers and collagen turnover increase with loading. Inflammatory cytokines can mediate increased collagen synthesis in tendon connective tissue and inflammatory

Q&A With Rodney Whiteley

1. *The last 25 years or so has seen an enormous shift in our understanding, and therefore management, of tendon, muscle and cartilage injury. This article in particular has discussed the role of anti-inflammatory medications, and the advice you are giving us now is more or less the exact opposite of what was thought to be best care a couple of decades ago.*

   Where do you think we are now in terms of our understanding? Are we close to being definitive on this topic, or are you expecting lots more changes to come over the next couple of decades?

   Sports science is constantly developing and no finding is definitive, it is always subject to a new scientific finding. However, I think that some inflammatory activity is needed for a physiological adaptive response to training, whether its muscle, bone or tendon.

2. *Being someone at the forefront of basic science research as well as regular clinical practice, could you gaze into your crystal ball and tell us what your hunches are for how the field of muscle, tendon and cartilage injury are going to change?*

   In my opinion, in the future we will use better imaging techniques and less invasive sampling techniques to be able to understand better what goes on in the tissue during sports injury and thus allow more targeted treatment. Further, individualised medicine/surgery will also come to sports science and we'll get better at characterising injury in the individual athlete.

3. *Your work points out that correct loading, i.e. appropriate exercise, seems to be our most powerful modifier of tendon. As a sports medicine practitioner, in a practical sense, how do you implement this intervention for your patients?*

   This means that whatever treatment modality you chose, mechanical loading of the tissue needs to be a part of it. In my view, there will be no pharmacological or surgical 'quick fix' in sports injury treatment of rupture and overuse that can work without mechanical loading. Even in severe injuries one should assure some physical activity loading of the injured tissue.

4. *What do you do when the player/coach/parent is adamant they want anti-inflammatories for their 'tendinitis'?*

   In some instances (if early inflammation is clear), I fully accept anti-inflammatory treatment, but I never let it stand alone and I don't get into a situation where I repeatedly give anti-inflammatories again and again.

5. *How do you deal with the athlete who sees you and wants to get an injection of glucocorticoids or other substances that can initiate tissue regeneration and inflammation?*

   In sports medicine some of our treatments are not evidence-based, but the important point is that you should always be aware when you are dealing with an undocumented treatment, and those who are subjected to that treatment should receive it in a controlled clinical trial. The dangerous thing is when your ethical standard drops and, due to pressure from the sports society or due to personal economical interest, you use treatments that are undocumented.

pathways regulate the exercise-mediated blood flow. Thus, anti-inflammatory treatment may inhibit physiological changes occurring in response to exercise. Chronic tendinopathy does not display any inflammation activity either at rest or after acute exercise, and thus the role of anti-inflammatory treatment may be minimal. In tendon rupture an early inflammatory response is seen, and studies on animals indicate that mechanical loading applied during regeneration of the tendon may modulate this response in a beneficial manner, whereas the guidelines for use of anti-inflammatory medication in relation to tendon rupture in humans are lacking evidence.

References available at www.aspetar.com/journal

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