Is inflammation harmless to loaded tendons?

THE ROLE OF INFLAMMATION in tendon pathology is controversial. Most pathological tendon conditions are due to overuse or degeneration, and they are claimed not to be of an inflammatory nature. Inflammatory cells are few in biopsies from, e.g., chronically painful and swollen Achilles tendons, and the term tenosynovitis for this condition has therefore been replaced by tendinosis. Tendinosis usually presents as localized intratendinous lesions, which are richly and pathologically vascularized, as visualized by ultrasound with Doppler technology. Histology is variable, with signs of degeneration, collagen breakdown, and repair. Granulation tissue and substance P nerve sprouting is seen (4). It is not until the condition has become chronic that surgery can be motivated and a biopsy taken. Although inflammatory cells may be only moderately increased in number at this stage, it is reasonable to assume that a stronger inflammatory reaction occurred in the earlier development of the lesion. Tendinosis tendons contain more granulation tissue than ruptured ones (4), but painful tendinosis is clinically not associated with an increased risk of rupture despite the compromised collagenous structure. This is counterintuitive; why don’t they rupture?

One would think that if a tendon is invaded by inflammatory cells, increased local levels of degradative enzymes such as matrix metalloproteinases (MMPs) would lead to rapid tissue degradation, making the tendon weaker. In a common experimental model for tendon injury, collagenase is injected into the vicinity of the tendon, and this can decrease its mechanical strength drastically in a few days.

In rheumatoid arthritis there is indeed inflammation around tendons, often leading to rupture, especially in the hands. During surgery, however, one can see pannus tissue invading deep into the tendon substance in local destructive lesions, while the remaining fasciculae of the same tendon segment look macroscopically intact and appear to function normally, despite the inflammatory environment. Often, the inflammatory tissue appears to penetrate the tendon by separating the fasciculae rather than by resorbing them. This suggests that tendons are relatively resistant to degradation by inflammation.

In this issue of the Journal of Applied Physiology, Marsolais et al. (1) address the issue of inflammatory cells and tendon destruction by using the classical method of injecting carrageenan locally. Carrageenan is a polysaccharide derived from seaweeds (a common food additive). It is named after the red algae “Irish moss,” called carragein in Irish. When injected, it appears to have no other effect than to be taken up by macrophages, which causes a granulomatous inflammation. Marsolais et al. (1) demonstrate that a single carrageenan injection led to infiltration of macrophages into the rat Achilles tendon structure with increased levels of the degradatory enzyme MMP-2 and a reduction of its inhibitors, tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2). Yet, no reduction in collagen content and the mechanical force at failure could be demonstrated (other mechanical properties were not reported). The authors then proceeded to in vitro experiments with rat tail tendons and demonstrated that a constant tension protected the tendon fasciculae from mechanical deterioration induced by macrophages in the medium. They suggest that acute inflammation does not damage intact collagen fibers and that this is because they are somehow protected by mechanical loading.

It has previously been shown that constant tension protects rabbit patellar ligaments in vitro from degradation by bacterial collagenase (3). This previous study also had data to suggest that the protective effect was not due to decreased collagenase diffusion, and it was speculated that stresses and strains of the extracellular matrix might modify the kinetics of the collagenase-collagen interaction.

Before jumping to the conclusion that inflammation is harmless to loaded tendons, there are three points to address. First, the in vivo Achilles tendon experiments of Marsolais et al. (1) were terminated after 3 days only. Even though this is enough time to demonstrate degradation by large doses of injected bacterial collagenase, it is a very short time in tendon metabolism. On the other hand, their somewhat briefly reported in vitro experiment suggests that even 24 h are sufficient for a measurable decrease in strength when unloaded tendon fasciculae are cultured together with macrophages. This is under in vitro conditions with thin fasciculae. The authors argue that in their Achilles tendons in vivo, a reparative response with fibrosis would make later time points than 3 days less likely to show weakening. This remains to be investigated. It cannot be excluded that a somewhat prolonged acute inflammation would lead to measurable deterioration of tendon integrity.

Second, the mechanical testing only addressed force at failure, which is technically a very difficult variable to measure, and an unknown number of tendons had to be discarded because they did not rupture in the tendon substance, but at the fastening devices of the testing machine. This study generally compares very small groups.

Third, the in vitro tension experiment only used constant stress, which is highly unphysiological. The model has an elegant simplicity, but in real life, tendons are subjected to variable cyclic loading and intermittent rest periods. Unless the low stress applied can be said to correspond to a resting state, the protective effect of constant load may therefore be biologically and clinically irrelevant. However, a protective effect also of intermittent loading may well exist, because in a previous in vitro study, moderate intermittent loading of tendon fibroblasts reduced their expression of inflammatory mediators and MMP-1 in response to IL-1β (7).

Marsolais et al. (1) injected 30 μl of carrageenan solution into the tendons. This corresponds to over one-third of the wet weight of the tendons from similar sized rats (own unpublished data). Because tendon is a rather stiff material, it is therefore likely that most of the injected carrageenan was not contained but ended up in the peritendinous tissues. Deliberate peritendinous injections have been used by others, still resulting in intratendinous pathology. Repeated injections of prostaglandin E1 led to acute intratendinous inflammation at 1 wk, followed by degenerative changes at 3 wk. This was suggested as a model for tendinosis (5). Unfortunately, no mechanical data were reported.

A perhaps more clinically relevant model uses the rat shoulder, which is surprisingly similar to human anatomy. Repeated carrageenan injections into the subacromial bursa led to not only bursal or subacromial inflammation but also macrophage
infiltration of the underlying supraspinatus tendon, with a deranged collagen structure and fibrocartilaginous metaplasia (6), possibly due to increased hydrostatic pressure. These changes were found after several weeks. Again no mechanical data were reported, but fibrocartilaginous metaplasia has been associated with supraspinatus tendon rupture.

These studies leave little doubt that peritendinous inflammation can lead to intratendinous pathology, at least in small experimental animals. The interesting and unexpected finding in the study by Marsolais et al. (1) is that this does not lead to weakening of the tendon, at least not during the very acute phase. Does this have relevance for tendon overuse injuries?

If intratendinous inflammation is rarely found clinically, acute peritendinous inflammation is common and would be detrimental if the tendons were highly susceptible to inflammation-driven degradation. Luckily, they appear not to be, and rupture after acute peritendinous inflammation is seldom an issue. In tendons with limited space, however, acute inflammation can cause irreversible intratendinous changes. One example is stenosing tenosynovitis of flexor tendons, the common trigger finger. This condition often develops after overload, followed by tenderness suggesting synovitis, before stenosing tendon nodules form and the trigger phenomenon appears. According to this author’s experience, a steroid injection into the tendon sheath in the early phase, when the trigger phenomenon is mild, can lead to rapid disappearance of all symptoms. Two placebo-controlled randomized studies confirm that this is correct (2). This appears to be an example of anti-inflammatory treatment preventing intratendinous structure changes. Yet, these changes do not lead to rupture.

Marsolais et al. (1) address the mechanical consequences of inflammation, and their findings differ from what many may have taken for granted. As always, when a new perspective is taken, many new questions are raised, and a first study cannot be comprehensive. It hopefully inspires more and better-powered studies of the connections between inflammation and tendon structure and mechanics, for example, a more thorough mechanical analysis, studies of the development of tendon strength over time during inflammation, and especially the effects of intermittent loading.

REFERENCES


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