Mysterious properties of tendon metabolism

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The paper in this issue by Christensen et al. (1) from the Danish Institute of Sports Medicine adds to our knowledge of the effects of decreases in physical activity on muscle and tendon and on the changes that occur on remobilization. However, many aspects of the results are counterintuitive and difficult to explain with our current views about alteration of tissue protein mass. Of course, for human tendon metabolism, our current knowledge is in fact very sparse, so maybe the difficulties themselves are simply the effect of ignorance.

What the Danish team did was to study patients who had broken the ankle of one leg and who provided an opportunity to study the effects of forced immobility of the injured lower leg for a period that would be hard to justify with healthy volunteers immobilized in a similar fashion. The noninjured leg was taken as a control, and indeed it seemed to show no perceptible changes in tissue mass over the period of the study: 7 wk of casting and a further 7 wk of recovery during rehabilitation. The changes in muscle size and tendon were determined by computerized tomography rather than by magnetic resonance imaging, which was ruled out by the presence of metallic fixing devices inserted during surgical repair.

The changes in the muscle were not particularly surprising: a decrease in calf muscle mass of ~4% per week and a somewhat greater decrease in muscle strength, 8%, reinforcing previous findings of greater functional than structural decreases in muscle during immobilization. The changes in muscle during remobilization were also similar to what might have been expected: a slow regaining of muscle mass and strength at about half the rate at which the loss had occurred. These findings reinforce the idea that to regain muscle tissue mass and function something more than letting nature take its course is needed to maximize recovery, and it would be interesting to see how much improvements could be achieved with resistance training added to routine physiotherapy.

So far so good: no surprises. What is surprising are the data concerning Achilles tendon. It might be expected that, like muscle, it would show a loss of mass and because most of the tendon material is collagen, that this might be achieved by decreases in collagen synthesis or increases in collagen breakdown. In fact, no change in tendon mass was observed either in the immobilized or remobilized phase, except for what appears to have been localized swelling a few days after injury. This result confirms that found for patella tendon in a much shorter (21 day) study of healthy young men who underwent unilateral leg suspension (2). In that study too, tendon mass fell but that was accompanied by a decrease in the rate of collagen synthesis measured directly by incorporation of stable isotopically labeled proline into tendon collagen hydroxyproline. The major puzzle here was how could collagen synthesis fall but tendon dimensions remain stable? In the study of Christensen et al. (1), the isotopic approach was not used, but instead an alternative procedure was applied: the measurement in body fluids of molecules thought to be markers of collagen turnover, such as the procollagen peptides released on processing of procollagen to tropocollagen [e.g., NH$_2$-terminal propeptide of type I collagen (PINP) as an index of synthesis] and fragments of collagen cross-linked collagen telopeptides [COOH-terminal telopeptide region of type I collagen (ICTP)] released during collagen breakdown as indexes of that process. Of course, measurements made of blood and urine are unlikely to give specific information about alterations in a particular body site, but the Danes attempted to overcome this problem by an elegant technique they developed: dialysis of the peritendinous space with assay of the collagen turnover markers in the dialysis fluid. The findings in serum and urine (increases in collagen synthesis marker both immediately after immobilization and during recovery, and no change in urinary breakdown markers) are difficult to interpret, possibly reflective changes in bone remodeling during healing. However the changes in peritendinous dialysate were not at all expected. Instead of the marker for collagen synthesis falling it raised fivefold after 7 wk of immobilization, and it remained higher than baseline in the control leg during recovery. The breakdown marker in the space around the tendon in the injured leg was also fivefold higher than control and remained double its presumed basal value after recovery.

How are we to interpret the findings? The most puzzling feature is of course the lack any change in tendon size at any time. We must presume that tendon composition changes, not only in terms of molecular species, cross-linking, collagen, and glycoprotein content etc. but possibly also in hydration. A rise in collagen turnover would make sense during recovery, and a rise in collagen breakdown would make sense during immobilization, but fitting the observed changes into a reasonable model is difficult. The authors point out that their peritendinous dialysate results may be contaminated with markers from healing ankle bone, but even so the pattern of the changes is puzzling, especially for collagen synthesis markers, which are obviously at variance with the findings of de Boer et al (2). It will be difficult to study the effects of immobilization on tendon in healthy volunteers for such a long period, but it looks like this needs to be done, together with more peritendinous sampling and also sampling of tissue for composition analysis, or indeed tendon metabolism will remain the Achilles heel of our current understanding.

REFERENCES