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Editorial Comment

JMNI special issue — Tendons: the connection between muscle and bone

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Tendons are located in series between muscle and bone where they principally function to transmit volitional forces to produce motion. They are exquisitely structured to fulfill their mechanical role, consisting of a hierarchical arrangement of longitudinally-orientated, tightly-packed, type-I collagen fibers which provide tendons with a consummate ability to resist tensile loads. While we are all aware of tendons and appreciate their contribution, tendons have been referred to as the wallflowers of the musculoskeletal system because of scant interest in them relative to the more popular neighboring muscle and bone[1]. Contributing to the limited research into tendinous tissue has been the historical view that tendons are relatively inert structures lacking significant biology due to their limited cellularity and vascularity. While an ever growing body of work over past decades has set about addressing misconceptions regarding tendon biology, it is generally accepted that our knowledge remains in its infancy. This Special Issue of the *Journal* brings together leaders from around the globe who are at the forefront of tendon research to discuss their work and, in some instances, provide original new findings. As you scan the list of titles, we hope that you are impressed by the breadth of research, both basic and clinical, which is thriving in many parts of the world, and are as excited to read this work as we were to guest-edit it.

Is a cure for overuse tendinopathy just around the corner?

The slow and steady progress of scientific knowledge can sometimes be disheartening to clinicians and patients looking for answers – despite millions of person-hours and research dollars, effective cures always seem to be just on the horizon. Research has taught us that a magic bullet or molecule, no matter how well characterized in the laboratory, is unlikely to reverse the recalcitrant, longstanding pathology which characterizes many chronic overuse tendinopathies. Nonetheless, clinical improvements, and sometimes complete resolutions, can occur even in longstanding cases, which suggests that tendon's intrinsic healing capacity and growth factor signaling can be optimized and perhaps improved upon (see Oryan and Moshiri[2]). Also in this issue, Hoksrund and Bahr[3] review current clinical evidence on injection therapies for tendinopathy, including sclerosing injections, platelet rich plasma and autologous blood. The authors remind us that despite the promising results, clinical acceptance appears to have outpaced an evidence base which is preliminary and fraught with methodological concerns.

Mechanical loading: collagen fatigue or proteoglycan remodeling (or both?)

Finding a way to identify and prevent overuse tendinopathies before they become chronic could revolutionize sports medicine. Several papers in this issue examine loading-induced tendon responses (see Heinemeier and Kjaer[4] and Thornton and Hart[5]), including pathological (see Andarawis-Puri and Flatow[6]) and therapeutic (see Scott et al.[7]). A key point is that the earliest events in overuse tendinopathy are not yet known – is it tenocyte driven or does matrix fatigue occur first (see Andarawis-Puri and Flatow[6]), and at what point does inflammation or pseudo-inflammation occur (see Backman et al.[8])? Fascinating work by Parkinson et al.[9] shows that large, hydrophilic proteoglycans are rapidly synthesized and degraded in tendon, demonstrating the importance of intrinsic, tenocyte-driven processes; they suggest that the presence of glycosaminoycans and their catabolic products (which are retained for some time through interactions with other components in the tendon ma-

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trix) may underlie the acute swelling experienced by tendons following a bout of mechanical loading. Conversely (or perhaps complementarily), Backman and co-workers[8] show that the peripheral and central nervous systems are involved in acute tendon loading responses. Peripherally, Substance P levels were elevated after only 1 week in overused Achilles tendon; this elevation preceded the development of tendinopathy at 3 weeks. The paper contributes further evidence to a model of tendinopathy in which local Substance P production is elevated, leading to both localized and widespread neurogenic inflammation with central sensitization. Most interestingly, tissue changes on the contralateral (non-loaded) Achilles tendon, including a trend to increased Substance P, were also observed.

What can we learn from animal models?

A lot! (see Dirks and Warden[10] in this issue for a discussion of different models available). However, translation into clinical practice is not always a given. Animal models are essential in evaluating new surgical techniques, including biologically augmented or tissue engineering strategies (see Shearn et al.[11]); Edelstein et al.'s[12] fine overview summarizes a career's worth of animal research work focused on the rotator cuff tendons. As a salient example of neuromusculoskeletal interactions in the rotator cuff, a cuff transection leads to widespread neurological effects including an apparently nerve-mediated fatty degeneration in the cuff muscles (see Edelstein et al.[12]). Despite decades of research into surgical repair techniques, the best surgeon's re-tear rates remain around 50%. Clearly, this remains an active and important area of research.

Some other salient examples of animal findings which have found their way into clinical practice (also summarized in Edelstein et al.[12]), are mostly negative, but are nonetheless important. These include: (1) avoidance of post-surgical NSAIDs where possible, due to their deleterious effects on tendon healing; (2) lack of support for radiofrequency energy treatment, and; (3) understanding the mechanism of diabetes-induced tendon degeneration (it causes glycation end products to accumulate in collagen fibers, reducing their mechanical properties). And many others which we encourage the reader to discover.

Where next, mad scientists?

Sadly, this special issue cannot summarize recent advances in tendon imaging, not to mention work by many other fine researchers which could not be covered here (our apologies, especially to those we know personally). MRI and ultrasound continue to reveal deeper and finer details of tendon pathology, which will surely help to bridge animal models with human studies, revealing new neuromusculoskeletal interactions of clinical relevance. In particular, the field of pain science and central sensitization phenomena remain largely unexplored with relation to tendons. Ultrasound-guided injection techniques (see Hoksrund and Bahr[3]) may promise the unprecedented ability to deliver emerging therapeutics in a highly localized manner. But, if we are giving the impression that a cure for patellar tendinopathy will be available in time for the next basketball season opens, we apologize. Much work remains, for which reason we thank our valued contributors, and encourage readers to find time to enjoy.

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