Latest developments in tendinopathy

Report on the 2\textsuperscript{nd} International Scientific Tendinopathy Symposium

The second International Scientific Tendinopathy Symposium (ISTS), held in Vancouver 27-29 September 2012, brought together sports medicine clinicians and basic scientists. It was a truly international event with delegates representing 11 countries. I was able to attend thanks to a bursary from the British Society for Matrix Biology.

The first (half) day of the meeting comprised small group discussions coordinated by Karim Khan, editor of the British Journal of Sports Medicine (BJSM). The aim of these discussions was to stimulate debate and form the basis of a consensus statement, to be published in the BJSM, identifying the current priorities in tendon research. The themes addressed included the role of inflammation in tendinopathy, the transfer of knowledge into clinical practice, functional outcome measures, imaging techniques and surgical approaches. The second and third days were filled with short talks and poster sessions spanning the pathogenesis, imaging, and treatment (from physical therapy to surgery) of tendinopathy. A workshop for physical therapists was held in parallel on the third day.

The central nervous system (CNS) and tendinopathy

Tendinopathy frequently affects the same structure in left and right limbs in both human \textsuperscript{[1]} and equine \textsuperscript{[2]} patients and evidence is emerging that the CNS signalling plays a role in this bilateral presentation. Bill Vincenzino (University of Queensland, Australia) reviewed the evidence that patients with lateral epicondylalgia (tennis elbow) show CNS changes. Affected patients demonstrate mechanical and thermal hyperalgesia (not only locally in unilateral cases but at the contralateral site and remotely on the ipsilateral site also), increased nociceptive flexion reflex and a reduction in endogenous pain modulation. Recently, Andersson et al \textsuperscript{[3]} reported bilateral histological changes in a model of unilateral tendon overuse and in Vancouver I presented a study showing bilateral acceleration of peritendinous mineralization following unilateral injury \textsuperscript{[4]}. These clinical and experimental findings support the possibility that CNS signalling contributes to bilateral tendon changes but, of course, they do not prove it. There is a pressing need for experiments to test this hypothesis directly.

The biomechanical hypothesis for tendinopathy

Patrik Danielson (Umeå University, Sweden) updated delegates on the evidence supporting the biomechanical hypothesis for tendinopathy. Tendon cells are capable of producing a range of signal substances believed previously to be restricted to neurons, including acetyl choline, catecholamines, glutamate and substance P (SP). Within tendons, receptors for these substances have been found on nerves, blood vessels and tendon fibroblasts themselves and an increase in receptor activity could explain the hypercellularity and increased angiogenesis featured in tendinopathy. As an example, Patrik’s student Ludwig (Backman) later presented evidence that SP could reduce apoptosis of tendon fibroblasts via an Akt pathway. The group has previously been shown that SP can stimulate proliferation of these cells \textsuperscript{[5]}
Inflammation revisited

In horses, tendinopathy is readily recognisable as an inflammatory condition (tendinitis) as it involves heat, pain and swelling of the affected structure\(^6\), but this is not the case for affected human patients. Indeed, in 2002 Khan et al\(^7\) argued that overuse tendinopathy which occurs in humans was a non-inflammatory, degenerative condition, on the basis that inflammatory cells were undetectable and that the available anti-inflammatory treatments had no effect beyond the short term. However, this opinion must be reconsidered as in recent years inflammatory cells such as lymphocytes and macrophages as well as inflammatory mediators have been identified within tendinopathic tissue\(^8\). Alex Scott (University of British Columbia, Canada) highlighted the relationship between mast cells, present in greater numbers in tendinopathic tissue, and tendon fibroblasts to which they can bind. Mast cells appear to influence tendon fibroblasts in many ways, such as by increasing their COX-2 expression, survival, proliferation and ability to contract a collagen gel, which led Alex to suggest that mast cell inhibitors may be a future therapy for tendinopathy. Similarly, Johnathan Rees (Defence Medical Rehabilitation Centre, Surrey, UK) argued that newer anti-inflammatory medications employed to treat the rheumatoid arthritis, for example anti-Tumour Necrosis Factor alpha, may have also have a role in tendinopathy treatment.

Genetic factors

Malcolm Collins’s group (University of Cape Town and the South African Medical Research Council, South Africa) studies the genetic factors predisposing to soft tissue injury, in particular anterior cruciate ligament rupture and Achilles tendinopathy\(^9\). Improved understanding of these factors could allow the risk factors for, and treatment of, injury to be personalized. In his talk, Malcolm outlined the evidence that gene polymorphisms associated with type V collagen production are associated with Achilles tendinopathy. By mass, type V collagen is a minor component of tendon but it intercalates with types I and III to play a role in fibril assembly and lateral growth\(^10\). The major isoform of type V collagen comprises two α1 (V) and one α2 (V) chains. This group have identified two forms (C and T) of the 3’ UTR (untranslated region) of the COL5A1 gene [which encodes the α1 (V) chains] which are, in general, expressed in either normal (C form) individuals or those affected by Achilles tendinopathy (T form). The mRNA stability of the T form is higher than that of the C form which, the group suggests, could lead to greater type V collagen production in individuals with Achilles tendinopathy\(^11\). In addition, Malcolm’s team have also shown that the COL5A1 3’ UTR contains a binding site for Has-miR-608, a microRNA molecule. MicroRNAs are short RNA sequences which bind to the 3’ UTR, fine tuning gene expression. Two forms of the mature Has-miR-608 (produced by the polymorphic MIR608 gene) can bind at this site and one of these forms is independently associated with chronic Achilles tendinopathy\(^9\). In his conclusion, Malcolm hypothesized that patients with tendinopathy demonstrate increased type V collagen production leading to altered structural properties and in turn altered biomechanical properties of their tendons.
Imaging studies

I was particularly interested to learn about ultrasound tissue characterization (UTC) developed by Hans van Schie, a veterinarian (UTC Imaging and Erasmus University Medical Center, both in the Netherlands and Monash University, Australia). This methodology uses a tracking device to record transverse ultrasound images at 0.2 mm intervals along the tendon length. A custom designed algorithm allows four echo patterns to be discriminated (from intact aligned fibers to amorphous material) and quantified. The technique, originally validated using isolated equine flexor tendons, was used in studies of human Achilles tendons reported at the symposium.

News on stem cells

Roger Smith (Royal Veterinary College, UK) reported on the treatment of naturally occurring equine superficial digital flexor tendinopathy with mesenchymal stem cells (MSCs). Although a large proportion of the cells injected were lost rapidly from the treated tendon to other body sites (approximately 75% within 24 hours) the results have been very promising. MSC-treated tendons showed improved structural properties and histological scores compared with saline treated controls. Most importantly perhaps, the re-injury rate was 27.4% which is approximately half that reported in in studies of other treatments.[12] Margaret Smith (University of Sydney, Australia) also reported significantly improved histological scores following treatment with MSCs but in an ovine model of infraspinatus tendon hemitranssection. Most interestingly, Margaret’s group found that improvement was only temporary when treatment was administered 2 weeks after transection but sustained (present at 52 weeks) when treatment was administered after 11 weeks. Perhaps the tissue is less vascular 11 weeks after surgery allowing the administered cells to persist for longer.

Surgical approaches

Results for several different surgical approaches to treat tendon rupture and tendinopathic pain were presented. Of note, Håkan Alfredson (Umeå University) reported the success he has had with an ultrasound guided ‘mini-surgery’ to treat midportion Achilles tendinopathy. The technique involves using either a needle percutanously or a scalpel via an open approach (similar results) to scrape of the ventral aspect of the Achilles tendon where an increase in blood supply is detected. Håkan reported satisfactory improvement in approximately 90% of patients including elite athletes[13]. How this technique works and fits with the biochemical and inflammatory changes we understand to occur in tendinopathy, raises many questions.

Conclusion and future plans

Overall, I found this meeting valuable. This was an ideal audience for my current work and I developed new ideas for future experiments. I also renewed contacts and put some new faces to names. On the last day Patrik Danielson and Alex Scott (chairs of the 1st and 2nd ISTS respectively) invited proposals for the third symposium and encouraged delegates to join the organizing committee. The focussed nature of this gathering and presence of key figures in the field mean this meeting is a ‘must attend’ for workers committed to tendinopathy research. I look forwards to 2014.