The International Scientific
Tendinopathy Symposium

"Neuronal and non-neuronal pathways in the tendon pathology continuum"

Umeå, Sweden, September 30 - October 1, 2010
Tendinopathy Symposium, Umeå, Sweden, 2010
“Neuronal and non-neuronal pathways in the tendon pathology continuum”

Organizers:

Umeå University
Dept. of Integrative Medical Biology, Anatomy, and
Dept. of Surgical and Perioperative Sciences, Sports Medicine

Umeå kommun
(Umeå City and Municipality)

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Tendinopathy Symposium, Umeå, Sweden, 2010
“Neuronal and non-neuronal pathways in the tendon pathology continuum”

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Local Organizing Committee
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Assist. Professor Alex Scott, Physical Therapy, University of British Columbia, Canada
Assoc. Professor Patrik Danielson, Anatomy, Umeå University

International Keynote Contributors/Advisors on Main Scientific Program
Professor David Hart, University of Calgary, Canada
Dr Graham Riley, University of East Anglia, United Kingdom
Assoc. Professor Jill Cook, Deakin University, Australia
Adjunct Prof. Craig Purdam, Australian Institute of Sport and University of Canberra, Australia
Dr Jamie Gaida, Monash University, Australia

Award Committee (Best Poster Award)
Professor Sture Forsgren, Umeå University (CHAIR)
Chair of Scientific Committee
sture.forsgren@anatomy.umu.se phone: +46 90 786 51 47
Assoc. Professor Jill Cook, Deakin University, Australia
Assist. Professor Alex Scott, University of British Columbia, Canada
## Program - Thursday September 30

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<td>09.30-09.45</td>
<td><strong>Opening of Symposium</strong> &lt;br&gt; Dr Patrik Danielson MD, PhD 5 Umeå University Sweden Symposium Chair</td>
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<td>09.30-09.40</td>
<td>Prof Bengt Järnvholm MD, PhD 5 Umeå University Sweden Dean of the Faculty of Medicine, Umeå University</td>
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<td>09.45-10.00</td>
<td><strong>Honorary Opening Lecture</strong> &lt;br&gt; Prof David A. Hart PhD, FCAHS 15 University of Calgary Canada Why Tendinosis – Does it have a single etiology or is it multifaceted? An overview and some new speculations</td>
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<td>10.00-13.00</td>
<td><strong>Session I: “Pathophysiology of tendinopathy”</strong></td>
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<td>10.00-10.05</td>
<td><strong>Chair</strong> &lt;br&gt; Prof Sture Forsgren MD, PhD 5 Umeå University</td>
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<td>10.05-10.20</td>
<td><strong>Keynote lecture</strong> &lt;br&gt; Dr Graham Riley PhD 15 University of East Anglia United Kingdom Matrix turnover and tendinopathy – the role of enzymes, both good and bad</td>
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<td>10.25-11.00</td>
<td><strong>Session I talks</strong> &lt;br&gt; Mrs Anna-Carin Lundin MD 10 Linköping University Sweden Trigger finger is a form of tendinosis &lt;br&gt; Dr Sarah L. Franklin PhD, BSc (Hons) 10 University of Oxford United Kingdom An investigation into platelet-rich concentrate as a useful tool for tendon repair: A biological study &lt;br&gt; Ms Salma Chaudhury MB, BChir, MA, MRCS 5 Botnar Research Center, Nuffield Orthopaedic Center United Kingdom Genetic profiles of changes underlying different sized human rotator cuff tendon tears</td>
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<td>Session II: Research forum – “Pain mechanisms and tendinopathy”</td>
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### Keynote lectures

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<tr>
<td>14.20-14.35</td>
<td>II:K1</td>
<td>Prof Kurt Å. Olsson PhD</td>
<td>Sweden</td>
<td>The Pain System: Something old – Something new</td>
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<tr>
<td>15.00-15.15</td>
<td>II:K3</td>
<td>Prof Christopher J. Fowler PhD</td>
<td>Sweden</td>
<td>Potential pharmacological approaches to the treatment of tendinopathies</td>
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### Session II talks

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<tr>
<td>16.00-16.10</td>
<td>II:1</td>
<td>Dr Steve Gwilym MD, PhD</td>
<td>United Kingdom</td>
<td>Shoulder impingement syndrome; Evidence that central sensitisation of pain processing influences clinical presentation and outcome following surgery</td>
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<td>16.15-16.20</td>
<td>II:2</td>
<td>Miss Hannah Oag MA, MBBS, MRCS</td>
<td>United Kingdom</td>
<td>Relationship of rotator cuff tears, shoulder pain and functional loss in a normal population</td>
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<td>16.25-16.30</td>
<td>II:3</td>
<td>Ms Lotta Willberg MD</td>
<td>Sweden</td>
<td>Patellar tendinopathy – good clinical results and new findings with ultrasound and Doppler-guided arthroscopic shaving</td>
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<td>16.35-16.40</td>
<td>II:4</td>
<td>Prof Sture Forsgren MD, PhD</td>
<td>Sweden</td>
<td>Effects on the contralateral tendon/muscle when the limb on one side is markedly overused – implications for tissue changes and pain?</td>
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### ROUND-TABLE DISCUSSION

- **Moderators:** P. Danielson, A. Scott
- **Panel:** D. Hart, J. Cook, G. Riley, E. Hansson, Kurt Å. Olsson, C. G. Fowler, H. Alfredson

### SYMPOSIUM GALA DINNER

19.30 - SYMPOSIUM GALA DINNER at the old Officers’ Mess in the former Garrison Houses of the Military Regiment (I20) of Umeå, in the presence of... the Vice-chancellor of Umeå University, Prof Lena Gustafsson, and the Co-Mayors of the City of Umeå: Mr Lennart Holmlund, City Commissioner and Chair of the City Executive Board, and Ms. Marie-Louise Rönnmark, City Commissioner and Chair of the City Council.
### Program – Friday October 1

(Joint session with conference for physiotherapists and GP:s)

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<td>MORNING COFFEE 30 min</td>
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<td>09.00-12.00</td>
<td><strong>Session III: “Frontiers in clinical tendinopathy research, and latest developments in clinical management of tendinopathy”</strong></td>
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<td>09.00-09.05</td>
<td>Prof Håkan Alfredson MD, PhD 5 Umeå University Co-chair: Dr Patrik Danielson</td>
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<tr>
<td><strong>Keynote lecture</strong></td>
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<tr>
<td>09.05-09.20</td>
<td>III:K1 Assoc Prof Jill Cook PhD 15 Deakin University Australia  Compression and tendinopathy</td>
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<tr>
<td><strong>Session III talks</strong></td>
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<tr>
<td>09.25-09.35</td>
<td>III:1 Dr Richard Murphy BA, MBChB 10 University of Oxford United Kingdom The development of an ultrasound-guided core needle biopsy technique for sampling rotator cuff tendon</td>
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<td>09.40-09.45</td>
<td>III:2 Dr Guillermo Alvarez Rey MD 5 AMS Sport Medicine Center, Malaga Ultrasound guided tenotomy of gluteus medius tendinopathy (GTPS): A difficult topic to treat</td>
</tr>
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<td>09.50-09.55</td>
<td>III:3 Dr Tomás F. Fernández Jaén PhD 5 Clinic CEMTRO, Catholic University Murcia Spain Clinical evaluation of ultrasound-guided percutaneous lavage as a treatment option for calcifying tendinopathy of the shoulder</td>
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<td>10.00-10.05</td>
<td>III:4 Dr Lorenzo A Masci MBBS, FACSP 5 Pure Sports Medicine, London United Kingdom Evaluation of conservative treatment program of partial tears of Achilles tendons based on new sonographic changes of partial tears: A pilot study</td>
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<td>10.10-10.15</td>
<td>III:5 Ms Nele Mahieu PT, PhD 5 Ghent University Belgium The effect of military training on the vascular response of the Achilles tendon: a prospective design in military recruits</td>
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<td>10.20-10.40</td>
<td>REFRESHMENTS 20 min</td>
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<td><strong>Keynote lecture</strong></td>
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<tr>
<td>10.40-10.55</td>
<td>III:K2 Adjunct Prof Craig Purdam FASMF, FACP (Sports) 15 Australian Institute of Sport &amp; University of Canberra Australia A mechano-transduction model for early reactive tendinopathy. Implications for clinical management</td>
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<td>III:9</td>
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12.00-13.00 **LUNCH** at Hotel Björken  
60 min

13.00-**Thesis Defence**

**Chair:** Prof Mikael Wiberg, MD, PhD  
*Professor of Anatomy and Hand Surgery, Umeå University*

**13.00- (~15.00) THESIS DEFENCE**

Dr Gustav Andersson, MD
Dept of Integrative Medical Biology, Anatomy, and Dept of Surgical and Perioperative Sciences, Sports Medicine, Umeå University  
Influences of paratendinous innervation and non-neuronal substance P in tendinopathy – studies on human tendon tissue and an experimental model of Achilles tendinopathy  
(Please, see separate announcement!)

~15.00 **COCKTAILS** served on the 9th floor with a spectacular view of the City of Umeå

**18.30-** **DISSERTATION PARTY** at Restaurant T.C. in the City Centre  
(Aperitifs from 18.30; dinner served at 19.30)
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<td>P-1</td>
<td>Dr Suzan De Jonge MD, MSc</td>
<td>Erasmus University Medical Center</td>
<td>The Netherlands</td>
<td>Platelet-rich plasma treatment in chronic Achilles tendinopathy: A double-blind randomised controlled trial with one year follow-up **</td>
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<tr>
<td>P-2</td>
<td>Prof Christopher J. Handley PhD, DSc</td>
<td>La Trobe University</td>
<td>Australia</td>
<td>Altered proteoglycan metabolism is a feature of human patellar tendinopathy **</td>
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<td>P-3</td>
<td>Ms Jessica Pingel PhD-student</td>
<td>University of Copenhagen</td>
<td>Denmark</td>
<td>Structural and physiological changes in tendinopathy **</td>
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<td>P-4</td>
<td>Mr Anders P. Boesen MD</td>
<td>University of Copenhagen</td>
<td>Denmark</td>
<td>Evidence of accumulated stress in Achilles and anterior knee tendons in elite badminton players (Poster at the symposium is cancelled, but the abstract can be found in the symposium booklet.)</td>
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<td>P-5</td>
<td>Ms Pernilla Eliasson MSc</td>
<td>Linköping University</td>
<td>Sweden</td>
<td>Mechanical stimulation of tendon healing: When and how? **</td>
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<td>P-6</td>
<td>Prof Malcolm Collins PhD</td>
<td>South African Medical Research Council &amp; University of Cape Town</td>
<td>South Africa</td>
<td>The COL5A1 gene and musculoskeletal soft tissue injuries **</td>
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<td>P-7</td>
<td>Prof Malcolm Collins PhD</td>
<td>South African Medical Research Council &amp; University of Cape Town</td>
<td>South Africa</td>
<td>Range of motion measurements diverge with increasing age for COL5A1 3’- Untranslated region genotypes</td>
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<td>P-8</td>
<td>Mr Christoph Spang Student</td>
<td>Umeå University</td>
<td>Sweden</td>
<td>Is glutamate signaling of importance for the musculoskeletal system? – studies on myositis in response to muscle overuse and injections into the loose paratendinous tissue of the Achilles tendon **</td>
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<td>P-9</td>
<td>Ms Salma Chaudhury MB, BChir, MA, MRCS</td>
<td>Botnar Research Center, Nuffield Orthopaedic Center</td>
<td>United Kingdom</td>
<td>Using FTIR to differentiate rotator cuff tears and identify treatment biomarkers</td>
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<td>P-10</td>
<td>Ms Salma Chaudhury MB, BChir, MA, MRCS</td>
<td>Botnar Research Center, Nuffield Orthopaedic Center</td>
<td>United Kingdom</td>
<td>Mechanical suitability of extracellular matrix grafts to augment repairs of human rotator cuff tears</td>
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<td>P-11</td>
<td>Ms Salma Chaudhury MB, BChir, MA, MRCS</td>
<td>Botnar Research Center, Nuffield Orthopaedic Center</td>
<td>United Kingdom</td>
<td>Dynamic shear analysis: A novel technique for comparing the shear mechanical properties of normal and torn rotator cuff tendons **</td>
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<td>P-12</td>
<td>Ms Salma Chaudhury MB, BChir, MA, MRCS</td>
<td>Botnar Research Center, Nuffield Orthopaedic Center</td>
<td>United Kingdom</td>
<td>Characterizing differences in the collagen structural composition between normal and torn rotator cuff tendons using differential scanning calorimetry</td>
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<td>P-13</td>
<td>Mr Ludvig Backman MSc, BSc (PT), PhD-student</td>
<td>Umeå University</td>
<td>Sweden</td>
<td>Characterization of human Achilles tendon cells in respect to effects of substance P stimulation in vitro</td>
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<td>P-14</td>
<td>Mr Ludvig Backman MSc, BSc (PT), PhD-student</td>
<td>Umeå University</td>
<td>Sweden</td>
<td>Endogenous substance P production increases with exercise in an animal model of tendinopathy – peptidergic elevation precedes tendinosis-like tissue changes such as cell proliferation and angiogenesis **</td>
</tr>
<tr>
<td>P-15</td>
<td>Dr Michael Posthumus PhD</td>
<td>University of Cape Town</td>
<td>South Africa</td>
<td>A potential link between Achilles tendinopathy risk and endurance running ability **</td>
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<tr>
<td>Poster</td>
<td>Presenter</td>
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<tr>
<td>P-16</td>
<td>Dr Michael Posthumus PhD</td>
<td>University of Cape Town</td>
<td>South Africa</td>
<td>The polygenic profiles in participants with Achilles tendinopathy and controls</td>
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<td>P-17</td>
<td>Dr Michael Posthumus PhD</td>
<td>University of Cape Town</td>
<td>South Africa</td>
<td>A pathway-based approach investigating IL-1B, IL-6 and IL1-RN provides new insight into the genetic susceptibility of Achilles tendinopathy</td>
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<tr>
<td>P-18</td>
<td>Mr Johan Bagge MSc, BSc (PT), PhD-student</td>
<td>Umeå University</td>
<td>Sweden</td>
<td>There is a morphologic correlate for autocrine/paracrine TNF-alpha effects in the human Achilles tendon. Particularly evident for tendinosis tendons **</td>
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<tr>
<td>P-19</td>
<td>Dr Tomás F. Fernández Jaén PhD</td>
<td>Clinic CEMTRO, Catholic University Murcia</td>
<td>Spain</td>
<td>Protocol CEMTRO for treatment of tendinopathy. Clinical study.</td>
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<td>P-20</td>
<td>Dr Tomás F. Fernández Jaén PhD</td>
<td>Clinic CEMTRO, Catholic University Murcia</td>
<td>Spain</td>
<td>Magnetic resonance imaging of the shoulders of the handball players **</td>
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<td>P-21</td>
<td>Mr Yafeng Song PhD-student</td>
<td>Umeå University</td>
<td>Sweden</td>
<td>Muscle overuse affecting the triceps surae and the Achilles tendon leads to bilateral changes in the muscle tissue of the triceps surae - Studies using a rabbit model **</td>
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<td>P-22</td>
<td>Ms Lina Renström Medical student</td>
<td>Umeå University</td>
<td>Sweden</td>
<td>Is TNF-alpha not only of relevance for diseased joints but also muscles and tendons? – Studies on expression of the TNF receptor type I in myositis **</td>
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<tr>
<td>P-23</td>
<td>Dr Charlotte Avella BVSc, PhD, Cert EP, Cert ES (orth), MRCVS</td>
<td>The Royal Veterinary College, University of London</td>
<td>United Kingdom</td>
<td>The influence of cyclical loading on equine tendon in vitro – Relevant lessons for the effects of in vivo exercise? **</td>
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**) Posters eligible for Best Poster Award

as decided by the Poster Award Committee Chair.

The Poster Award Committee will visit each of the eligible posters, in consecutive order as numbered, during the Poster Session. The presenting author should be at his/her poster at that time, and everyone is given 2 minutes each to present his/her poster.

The Committee will convene after Session II for a decision. The winner will be announced at the Symposium Gala Dinner on Thursday night. The Prize Sum is 150 €.
HONORARY OPENING LECTURE:

WHY TENDINOSIS – DOES IT HAVE A SINGLE ETIOLOGY OR IS IT MULTIFACETED?
AN OVERVIEW AND SOME NEW SPECULATIONS

Hart DA

McCaig Institute for Bone & Joint Health, University of Calgary, Calgary, Alberta, Canada

INTRODUCTION

Tendons are a heterogeneous group of structures which normally function in an active biomechanical environment at ~40-50% of their ultimate tensile strength. They are comprised of collagens (collagen I, III and V) and other matrix molecules, as well as a subset of cells (tenocytes, mast cells, neural elements, microvascular cells). The ECM of tendons and their cellular complement varies along their length and there are also species variations, with some tendons from species such as the mouse becoming mineralized during the aging process. Thus, tendons are very heterogeneous, and are likely uniquely designed to operate within specific mechanical environments.

TENDINOSIS

While tendons are diverse and heterogeneous, they can suffer overt trauma with rupture or a chronic and often times, painful sub-acute loss of function termed tendinosis. Interestingly, tendinosis can arise in specific areas of tendons, but an analogous “ligamentosis” in ligaments has not been described. Ligaments are passive structures which operate in low load mechanical environments. Tendinosis is usually characterized by a lack of exogenous inflammatory cells, although abnormal concentrations of cells such as mast cells and neural elements and their associated neuropeptides, as well as tenocytes are present along with an abnormal ECM. Some derangements of the above are not associated with pain, and thus can precede development of overt symptoms. Tendinosis can develop in specific tendons of a subset of athletes engaged in specific sports, is more common in males than females, and can reproducibly occur in specific areas of tendons.

TENDINOSIS ETIOLOGY

The development and progression of tendinosis may be comprised of two central elements, 1) excessive biomechanical use of the tendon (exceeding the threshold of subclinical disruption of tendon integrity; e.g. overuse syndrome), and 2) a chronic dysregulation of the endogenous biological repair process required to maintain such integrity leading to an abnormal repair phenotype. Why only a subset of people engaged in a specific activity develop tendinosis may, in part be attributed to biomechanical factors related to intensity and duration of tendon use, style and appropriateness of the biomechanical stimulation, as well as the genetics of normal ECM composition and function (induction of damage to tendon integrity). As well, biological variation in initiation of acute and chronic aspects of the repair process plus genetic variation in such response phenotypes may contribute to the failure to repair and resolve the response to local injury (acute subclinical repair vs a chronic fibrogenic response phenotype). Recent studies, in a variety of injury response models and in humans, have indicated that such chronic fibrogenic responses affect a subset of people following overt injury and a “neural-mast cell-myofibroblast” axis is likely involved in many different clinical situations. Elements of such an “axis” have been shown to be altered in studies from our lab and those of our collaborators in overtly injured tendons undergoing normal repair, as well as those exhibiting features of tendinosis. The central driver of this postulated “axis” may be the neural component, but in all likelihood the axis is not linear or unidirectional, but instead is functionally multidirectional based on results of pharmacological interventions designed to disrupt the abnormal axis in a fibrogenic environment. In this regard, the neural component may be considered the vehicle for neurogenic inflammation rather than exogenous inflammatory cells.

SUMMARY

Tendinosis may be considered to have two major components, with induction associated with biomechanically-mediated disruption of tendon integrity (sub-acute injury), followed by a non-resolving endogenous fibrogenic response to such injury (deviated repair phenotype). With the recent finding of new pharmacologic approaches to reinitiate effective repair, additional options to study tendinosis progression and resolution via intervention at the level of the “nerve-mast cell-myofibroblast” axis to yield a more normal repair phenotype may yield effective treatments for patients with tendinosis in the future.
KEY NOTE LECTURE 1, SESSION I:

MATRIX TURNOVER AND TENDINOPATHY – THE ROLE OF ENZYMES, BOTH GOOD AND BAD

Riley G

University of East Anglia, UK

[Abstract will be delivered during the symposium.]
INTRODUCTION
At surgery for trigger finger, the tendons often appear swollen, with loss of natural colour and lustre. It is widely considered that the major pathology lies in the A1-pulley. There are many publications concerning pulley pathology and histology, but all papers in PubMed about tendon histology in trigger fingers were written before the tendinosis concept became accepted.

We hypothesized that trigger fingers would show similar histopathology as tendinosis in the e.g. Achilles tendon.

METHODS
We took 39 Biopsies from FDS and FPL tendons during surgery for trigger finger and 10 control biopsies from FPL and FDS during surgery for other reasons. They were given a random identity number for blinding, prepared for histology, sectioned parallel to the longitudinal axis of the tendon, and stained on separate glasses with Van Gieson (VG), Hematoxyllin & Eosin (H&E) and Alcian blue (ABl)

Two investigators independently analyzed the material under light microscope in a blinded fashion.

The VG glasses were classified as normal or not normal.

The H&E and Abl glasses were analyzed using a semi quantitative grading scale, the Movine score, with separate assessment of fibre structure, fibre arrangement, rounding of the nuclei, regional variations in cellularity, increased vascularity, decreased collagen stainability, hyalinization and glucosaminoglycan (GAG) content. We chose to not score increased vascularity because of the small size of our biopsies, and not the degree of hyalinization which has been shown to be poorly reproducible. The total histological score for a given slide could vary between 0 (normal) and 18 (the most severe abnormality).

RESULTS
We analyzed 39 VG glasses (10 glasses were excluded because of poor quality: 6 trigger fingers, 4 controls). Two independent investigators came to identical classification of all specimens: all 6 control tendons were rated as normal, and 30 of the 32 trigger fingers were considered not normal.

We analyzed 38 H&E and Alb glasses (11 glasses were excluded because of poor quality: 7 trigger fingers, 4 controls) using the modified Movin score. The mean score for the trigger finger material was 13.5 (SD 4.1) and for the normal material 0.17 (SD 0.4).

DISCUSSION
There was a histological picture resembling Achilles tendinosis in the analyzed trigger finger biopsies, but not in the control material. The material is small and only two of the biopsies in the control material were harvested under the A1 pulley at the site of trigger finger pathology. The other control biopsies had to be taken at a slightly more distal site. We had to modify the Movin score but still, there were tendinosis-like changes in the trigger finger biopsies with a general pattern of degeneration, such as waviness, loss of parallel arrangement and haphazard arrangement. There were also rounded cell nuclei, regional variations in cellularity, loss of collagen stainability, and increased ABl blue staining of GAGs. The question is whether this is a result of the proposed stenosis of the A1 pulley or whether the pathology described for the pulley is secondary to tendon swelling and tendinosis.

In conclusion, the histopathology in trigger finger is similar to that of Achilles tendinosis

REFERENCES
AN INVESTIGATION INTO PLATELET-RICH CONCENTRATE AS A USEFUL TOOL FOR TENDON REPAIR: A BIOLOGICAL STUDY

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INTRODUCTION
Platelet-rich concentrate (PRC) in the investigation of tendon healing and repair is currently an area of considerable interest. Upon activation, platelet alpha granules release a high concentration of growth factors which play an essential role in tissue healing.

Little is known about the exact mechanism of action of PRC in tendon healing, and even less is known about its role in the challenging environments found in damaged tendons, or its direct molecular and functional effects on tendon cells (tenocytes). The aims of this biological study were to investigate the potential role of PRC in promoting healing by enhancing migration, protecting tenocytes from stressful environments, and increasing tenocyte proliferation rate and survival by activating relevant signalling pathways.

The biological characteristics of PRC are being studied in conjunction with a clinical trial, where a randomised controlled study is utilized with the aim of determining the clinical efficacy of PRC in Achilles tendon ruptures, providing novel ultrasound functional imaging as a tool for tendon surgery outcome measurement.

METHODS
Centrifuged PRC, from fresh human whole blood, was immediately clotted and left in medium overnight to release biological factors. The pro-survival efficacy of PRC was examined following hypoxia (0.1% O₂), ciprofloxacin and dexamethasone treatments. Cells were treated for 72hrs with varying concentrations of PRC-conditioned medium and assessed for viable cell number (Live & Dead™ stain or Alamar Blue™) and proliferation (BrdU incorporation). Migration of tenocytes was assessed using a wound healing scratch assay. Activation of kinases was screened using a phospho-kinase array and activation of ERK and Akt pathways was confirmed by Western blot.

RESULTS
Viable cell number was significantly increased in a dose- and time-dependent manner by 2-10% PRC after 72hrs of treatment and DNA synthesis was significantly stimulated with 10% PRC. PRC significantly reduced the percentage of dead tenocytes (20% to 8%) cultured under hypoxic conditions at 48hrs. PRC also significantly reduced the number of dead cells with the addition of ciprofloxacin and prevented the dexamethasone-induced decrease in cell number.

A dose-dependent stimulation of migration was seen after 3 days of treatment with PRC. At the highest investigated concentration (10%) repopulation density was increased by 3 fold. ERK and Akt phosphorylation was strongly stimulated by treatment with PRC for 5mins, and remained high after a 30min application time.

DISCUSSION
Our in vitro results demonstrate several mechanisms by which PRC may act in vivo in the environmentally compromised conditions of a healing ruptured tendon. The prevention of hypoxic cell death may be an important function of PRC in promoting tendon healing. The study of ciprofloxacin and dexamethasone is of strong clinical interest as the use of these drugs is associated with a sharply increased risk of tendon rupture. PRC also has the potential to enhance wound healing by boosting cell proliferation and enhancing migration. Pro-survival and pro-proliferative kinases ERK and Akt are strongly activated by PRC, indicating two of the possible signalling mechanisms in tenocytes. The above detailed biological data, combined with preliminary clinical results, indicate that PRC has a positive role in promoting regeneration of ruptured Achilles tendon, and may lead to faster healing and reduce the re-rupture risk.

REFERENCES
GENETIC PROFILE OF CHANGES UNDERLYING DIFFERENT SIZED HUMAN ROTATOR CUFF TENDON TEARS

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INTRODUCTION
There is increasing evidence for a multi-stage model of rotator cuff (RC) tendon tears, wherein healing is affected by tear size. The underlying pathophysiology however is not fully understood. Changes in the production and remodeling of the RC extracellular matrix (ECM) are likely to be important determinants of RC tendinopathy as they affect healing and the ability to bear loads.

This study aimed to gain greater insight into size related tear pathogenesis by analyzing gene expression profiles from normal, small and massive RC tears.

METHODS
The genetic profiles of 28 human RC tendons were analyzed using microarrays representing the entire genome. 11 massive and 5 small torn RC tendon specimens were obtained from tear edges intraoperatively, and compared to 12 age matched normal controls. Semiquantitative real-time polymerase chain reaction (RT-PCR) and immunohistochemistry were performed for validation.

RESULTS
Numerous insightful gene changes were detected. Key changes included upregulation of aggrecan in massive tendon tears compared to normal controls, but not in small tears (p < 0.05, > 2-fold change). Matrix metallopeptidases (MMP)-15, -25 and a disintegrin and metallopeptidase (ADAMs)-15 were significantly downregulated in all tears. RT-PCR and immunohistochemistry confirmed altered gene expression.

DISCUSSION
The gene profiles of normal, small and massive RC tear groups suggested they are biologically distinct groups. This study identified a key role for ECM genes such as MMP-15, -25 and ADAMs-15 in RC tear pathogenesis, with aggrecan playing a specific role in massive RC tears. Modulating these ECM pathways may be a useful treatment strategy for improving clinical outcomes.
INTERACTION OF TENDON DERIVED FIBROBLASTS WITH COMMERCIAL AND NOVEL SUTURE MATERIALS – A COMPARATIVE STUDY

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INTRODUCTION
The supraspinatus tendon tears are a common and often debilitating condition. Currently, the most common surgical treatment is repairing the tear with non-absorbable sutures. However, it is of grave concern that a large proportion of technically correct surgical repairs re-rupture (1). Moreover, a number of studies have shown a beneficial effect of using a patch to augment repairs.

In this comparative study, we tested the compatibility of a novel suture and commonly used commercial sutures with human supraspinatus tendon-derived cells. Absorbable, non-absorbable and a novel silk suture (Spidrex) were studied, and the survival, proliferation and migration of tendon-derived fibroblasts on these sutures were used to evaluate their potential use for supraspinatus repair (2, 3).

METHODS
Tendon derived cells were extracted from human supraspinatus and foot flexor tendon by explantation and expansion. Cells were seeded on woven mats of sutures. Proliferation was measured as a function of metabolism, using an AlamarBlue Assay. The number of viable cells attached to sutures at different time points was measured using Calcein AM stain. DNA quantity, used as a surrogate for biomass and to validate proliferation assays was measured using pico green. Whilst growing on the sutures, cells were fixed and stained with DAPI/ActinPhalloidin and viewed using a fluorescence microscope to evaluate spreading and morphology on the sutures. Fluorescence imaging was also used to view direct migration from tendon explants to sutures.

RESULTS
Short-term studies demonstrated excellent cell attachment and survival on Spidrex and Ethibond more than any other tested suture. Vicryl showed the poorest cell growth and survival over short and long term. Moreover, proliferation assays showed that the degradation products of Vicryl had a negative effect on cell proliferation Coating sutures with collagen enhanced cell attachment and growth on all sutures.

Imaging showed that tendon-derived cells had excellent affinity to Ethibond (polyester) sutures. Cells easily attached and spread on the sutures, even when migrating directly from tendon explants (Figure 1).

DISCUSSION
The different sutures demonstrated varying interaction with cells in terms of attachment, growth, survival and migrations. Out of all sutures tested in this study, Vicryl showed the poorest performance as cell substrata, while Ethibond followed by Spidrex showed the best long-term interaction with cells in vitro. Whilst the novel suture Spidrex offers the advantage of being degradable, it is a novel material with no clinical history, requiring further studies in vivo to prove its safety.

These characteristics of sutures may be important for tendon repair after surgery. Overall, this study presents a quantitative comparison of commercial sutures as well as an in vitro evaluation system of new materials and constructions for tendon repair.

REFERENCES
KEY NOTE LECTURE 2, SESSION I:

ROLE OF MAST CELLS IN TENDON EXTRACELLULAR MATRIX REMODELING

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OBJECTIVES
The purpose of this study was to determine whether administration of a mast cell inhibitor (sodium cromolyn, SC) would influence tendon repair and extracellular matrix gene expression following acute injury.

METHODS
CD1 mouse patellar tendons were unilaterally injured and mast cell prevalence was determined. The effect of SC injection on tendon hypercellularity, cross-sectional area, collagen organization, and expression of extracellular matrix-related genes was examined.

RESULTS
Mast cell prevalence was markedly increased in injured patellar tendons ($p=0.009152$), especially at 8 weeks post injury ($p=0.025$). SC injection increased collagen organization compared to uninjected animals at 4 weeks and attenuated the development of tendon hypercellularity and tendon thickening post-injury. Expression of CTGF, ADAMTS1 and TIMP3 in injured tendon was reduced in the SC group.

CONCLUSION
SC injections moderated the structural alterations of healing tendon in association with downregulation of several genes associated with tendon fibrosis. This work corroborates previous findings pointing to a potential role of mast cells in tendon repair, and suggests that mast cell inhibitors could represent a possible therapeutic strategy for injured tendon.
KEY NOTE LECTURE 3, SESSION I:

THE INCREASED RISK OF TENDINOPATHY ATTRIBUTABLE TO TYPE 2 DIABETES: SUGAR, CYTOKINES OR OXIDATIVE STRESS?

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Individuals with type 2 diabetes mellitus (T2DM) have elevated risk of developing tendinopathy [1-4] and have worse treatment outcomes [5-8] than non-diabetics. The Achilles tendon of people with T2DM are thicker [9], have increased volume [10] and are less elastic [11]. Our recent research showed that individuals with Achilles tendinopathy had lipid profiles characteristic of insulin resistance [12]; insulin resistance (IR) is the key metabolic factor underlying T2DM [13]. In support of this finding, patients with rotator cuff tears had fasting glucose levels in the upper range of normal that were significantly higher than similar patients presenting with meniscal tears [14]. We await definitive studies measuring IR with gold-standard techniques.

The mechanisms underlying the association between IR and tendinopathy are poorly understood although vascular biology literature can provide useful insights. We have identified three interesting mechanisms whereby IR may contribute to tendinopathy. One, advanced glycation end product formation is accelerated by hyperglycaemia [15] and is hypothesised to promote tendon stiffening. Two, cytokines that are released from adipose tissue contribute to IR but may also have a direct effect on tendon cells – e.g. TNF-alpha (Gaida et al, submitted). Three, mitochondrial oxidative stress caused by nutrient overload (i.e. hyperglycaemia) is a key trigger for a protective mechanism (i.e. insulin resistance) to limit further nutrient delivery to the stressed cells [16, 17]. Tenocytes experiencing oxidative stress [18] may be less capable of appropriately adapting to changes in tendon loading. Tendinopathy research exploring these mechanisms may reveal novel treatment approaches, marking this as an area of strategic priority.


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SEQUENCE VARIANTS WITHIN THE 3'-UNTRANSLATED REGION OF THE COL5A1 GENE ALTERS mRNA STABILITY IN PATIENTS DIAGNOSED WITH CHRONIC ACHILLES TENDINOPATHY

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INTRODUCTION

Chronic Achilles tendinopathy (AT), a painful injury resulting from repetitive mechanical loading during certain occupational and sporting activities, is multi-factorial in nature, involving both extrinsic and intrinsic factors. Recently, a genetic component to the aetiology of the disease was identified. Specifically, variants within the 3'-untranslated region (UTR) of the COL5A1 gene were found to be significantly associated with AT in a South African (1) and an Australian (2) cohort. COL5A1 encodes the pro-α1 chain of type V collagen, a minor fibrillar collagen modulating fibrillogenesis. This study aimed at providing functional evidence for the initial genetic associations. The 3'-UTR region of the gene may contain regulatory units that could be affected by the polymorphisms. We hypothesise that sequence variants within the 3'-UTR region of the COL5A1 gene alter expression of the protein in patients using post-transcriptional mechanisms targeting mRNA stability. The objective of this preliminary study was to compare the effect of the 3'-UTR of COL5A1 from AT patients, with the at risk genotypes, on luciferase reporter gene activity to that of the wild type 3'-UTR, cloned from asymptomatic individuals.

METHODS

Total genomic DNA from Caucasian patients diagnosed with chronic AT and asymptomatic subjects had previously been extracted. The entire 2.5 kb of the COL5A1 3'-UTR from 4 patients and 3 asymptomatic subjects with the appropriate genotype, were amplified using nested PCR and cloned within the pGL3-Promoter vector, substituting the SV40 late poly (A) signal of the firefly luciferase reporter gene. The constructs were transiently co-transfected with an internal control, pRL-TK, into the human fibrosarcoma cell line HT1080. The normalised results were expressed as relative luciferase activity.

RESULTS

Inter-individual variation was demonstrated with a 2.6-fold difference (p<0.0001) in the highest activity for tendinopathic patient (110.5 ± 11.6 %, N=6) and the lowest activity for the asymptomatic subject (42.8 ± 8.6 %, N=6). In addition, an overall significantly higher activity (87.5 ± 11.6 % vs 67.6 ± 11.6 %, N=30, p<0.0001) was observed for the clones of the tendinopathic patients.

DISCUSSION

Inter-individual variation was present with an overall increase in mRNA stability for the tendinopathic patients. The COL5A1 3'-UTR may play an important role in the pathology of AT.

REFERENCES

THE GDF5 and TGFB1 GENES AND THE RISK OF ACHILLES TENDINOPATHY AND ACHILLES TENDON RUPTURE

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INTRODUCTION
Achilles tendinopathy and Achilles tendon rupture are multifactorial conditions for which various risk factors, including genetic factors, have been identified. Gene transfection of two members of the transforming growth factor-beta (TGF-β) family, TGF-β1 and GDF-5, have been shown to enhance tendon repair and mechanical strength within animal Achilles tendon injury models (1,2). The objective of this study was to investigate whether two functional 5’UTR single nucleotide polymorphisms (SNPs), the TGFB1 rs1800469 variant and the GDF5 rs143383 variant were associated with Achilles tendinopathy and/or Achilles tendon rupture (ATP) within an Australian (AUS) and a South African (SA) case-control cohort.

METHODS
171 subjects (58 AUS and 112 SA) subjects with Achilles tendon pathology (ATP), which includes 132 (59 AUS and 73 SA) subjects with Achilles tendinopathy and 39 with Achilles tendon ruptures (all SA), and 235 (142 AUS and 96 SA) asymptomatic control (CON) subjects were genotyped for the selected SNPs using custom designed Taqman® assays. A chi-squared (χ²) analysis or Fisher’s exact test was used to analyse any differences in the genotype and allele frequencies. Significance was accepted when P<0.05.

RESULTS
The genotype frequencies of the groups of subjects with Achilles tendinopathy and Achilles tendon rupture were similar and were therefore combined. There were no significant TGFB1 rs1800469 genotype (P=0.491) or allele (P=0.400) frequency differences between the ATP group and the CON group. The TT genotype of the GDF5 rs143383 variant was significantly over-represented in the ATP group of the AUS cohort (P=0.011; OR=2.24; 95% CI, 1.21–4.16), and when the AUS and SA cohorts were combined (P=0.004; OR=1.82; 95% CI, 1.23–2.74).

DISCUSSION
In conclusion, this study suggests that individuals with a TT genotype of the functional GDF5 rs143383 variant have twice the risk of developing Achilles tendinopathy and Achilles tendon rupture. This finding highlights a role of GDF-5 in the pathogenesis of Achilles tendon pathology. The GDF5 rs143383 variant, with other genetic variants that have been associated with Achilles tendinopathy and/or Achilles tendon rupture, should be incorporated in multifactorial models developed to identify athletes at increased risk.

REFERENCES
APOPTOSIS IN FULL-THICKNESS TEARS OF THE SUPRASPINATUS TENDON

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INTRODUCTION
Recent research has indicated that apoptosis plays a role in rotator cuff tendinopathy. However, the actual extent of tenocyte apoptosis in the torn supraspinatus, the accompanying subscapularis, and normal healthy tendon is currently unclear. The aim of this study was to quantitate the rate of tenocyte apoptosis in torn supraspinatus tendons and in the accompanying subscapularis tendons compared to a reference group of subscapularis tendons from patients with normal rotator cuffs. In addition, we aimed to determine the tenocyte density, proliferation rate, apoptosis rate and p53 expression pattern in these tendons.

METHODS
Tissue samples of torn supraspinatus tendons and intact, accompanying subscapularis tendons were harvested from 15 patients undergoing arthroscopic rotator cuff repair. In 10 patients undergoing arthroscopic repair of labral tears a reference biopsy of the intact subscapularis was harvested. Nicotine users were excluded since nicotine may enhance apoptosis.

For histology and immunohistochemistry, tissue samples were fixed in fresh 10% buffered formalin for 16-24 hours at 4°C and then subsequently dehydrated and paraffin embedded; tendon samples were oriented longitudinally and muscle samples transversely. For the examination of tendon degeneration and tenocyte density 5 μm sections were stained with hematoxylin and eosin (H&E) for morphology and with Alcian Blue for sulphated glycosaminoglycans (GAG). Ki67 immunohistochemistry was used to define the tenocyte proliferation rate. A monoclonal antibody against single stranded DNA breaks (F7-26; Chemicon, Temecula, California, USA) was used to examine apoptotic cell death and determine the apoptotic index. To further verify apoptotic cell death we examined the presence of p53. p53 is a powerful tumor suppressor and promotes programmed cell death following the apoptotic pathway.

RESULTS
The mean age of the patients with rotator cuff tear was 57.7 years (range 49 to 69). They were 10 men and 5 women. The mean age in the control group was 43.9 years (range 32-51); they were 5 women and 5 men. The biopsy specimens from torn supraspinatus tendons consistently revealed tendinosis. There was a significant increase of cell density (p<0.05) in the torn supraspinatus compared to the reference subscapularis tendons. The Ki67 immunohistochemistry showed a significantly increased proliferation rate in the torn tendons (p<0.05). There was a significant difference between the apoptotic index in torn supraspinatus and accompanying subscapularis compared to reference subscapularis tendons revealed by F726 immunohistochemistry(p<0.05). Pearson’s correlation coefficient confirmed a significant, positive correlation between the presence of apoptosis in torn supraspinatus and accompanying subscapularis (R²=0.5742; p=0.0005). P53 immunohistochemistry showed a significant greater expression in patient supraspinatus than in reference subscapularis (p<0.05).

DISCUSSION
The torn supraspinatus tendon is characterized by tendinosis, increased cell density, increased proliferation rate and increased apoptosis. This may indicate that apoptosis is the result of a failed repair process rather than the cause of tendon failure. The increase of apoptosis in both the torn supraspinatus and the accompanying subscapularis may indicate a general affection of the rotator cuff.
TEMPORAL RESPONSE OF TENDONS TO RACING AND TRAINING LOADS: QUANTIFYING ADAPTIVE CHANGES USING ULTRASOUND TISSUE CHARACTERISATION

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INTRODUCTION
Tendons are responsive to load; the type and amount of load influences the tendon’s response (Kjaer, 2004). Studies in vitro have shown that the presence of mechanical stimuli can affect the gene expression and protein production in tenocytes and are responsible for changes in the extracellular matrix of the tendon. However, detecting tendon response to load in vivo has been problematic.

Ultrasound technology that uses a correlation algorithm may allow for the detection of early and minor responses to load. The technology, ultrasound tissue characterization (UTC), takes 600 axial ultrasound images of the tendon over 12cm (Bosch, et al 2009). These slices are the constructed into a continuous image and the correlation of pixel brightness between slices is analysed. Four types of correlation are detected; fully aligned structures, two levels of less structural integrity, and a lack of echo due to the absence of ultrasound reflection. These four levels are quantified and have been used to determine changes in tendon structure after injury and during repair (Bosch et al, 2009)

This study is the first to attempt to quantify the tendon’s response to racing and training loads in terms of its structural integrity. This study will allow us to understand how and when tendons respond to load, which has implications for both human and equine athletes.

METHODS
A group of clinically sound thoroughbreds currently in training will be used for this study. Horses will be tracked over a two-week period using a combination of a training diary (incl. method of training, training surface, weather conditions etc) and GPS tracking devices (quantify speed and distance) to quantify training loads. The superficial digital flexor tendon (SDFT) of both forelimbs will be scanned using UTC each day allowing for the detection of adaptive changes in the tendon. UTC imaging will be correlated to training data to assess the influence different training loads have on tendon response. Horses that compete in a race will be scanned pre-race and at 24, 48 and 72 hours to detect when these changes occur in response to maximal loads.

RESULTS
Preliminary results suggest that using UTC, subtle adaptive changes can be detected in response to maximal load. Early evaluation also suggests response to load is dependent on a number of as yet undetermined factors which results in varying response to load. A group of horses have been shown to be unresponsive to racing loads whereas another group have shown a loss of structural consistency in response to maximal loads.

DISCUSSION
Understanding how and when tendons respond to load will be benefical to the equine industry and will allow the development of training programs and screening methods to minimize the risk of tendon injury. The use of UTC in the clinical setting may also allow for the detection of sub-clinical tendon injury due to its ability to detect subtle changes in the structural consistency of the tendon.

REFERENCES
A ‘BIOCHEMICAL MODEL’ FOR TENDINOPATHY PATHOLOGY
– WHAT IS THE ROLE OF NON-NEURONAL SIGNAL SUBSTANCES IN CHRONIC TENDON PAIN AND STRUCTURAL TISSUE CHANGES, AND HOW DO WE TEST IT?

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INTRODUCTION
Studies of recent years on human tendinopathies have provided us with evidence of a local, non-neuronal production in tendon cells (tenocytes) of signal substances traditionally confined to neurons. These biochemical mediators include acetylcholine [1], catecholamines [2], substance P [3], and glutamate [4]. Furthermore, the receptors for several of these substances have been found on nerve fascicles and in blood vessel walls, as well as on the tenocytes themselves, of the tendon tissue. The findings provide the basis for locally produced signal substances to influence pain signalling, angiogenesis, and/or structural tissue changes in tendinopathy, including degenerative-like changes (tendinosis). This reinforces a previously presented ‘biochemical’ hypothesis [5] for tendinopathy, suggesting that biochemical mediators in the tendon tissue might influence/irritate nociceptors, in or around the tendon, to cause chronic tendon pain. These theories now need testing in experimental models. We are currently using two models: An experimental animal model for Achilles tendon overuse [6], and a model of culturing human tendon cells.

METHODS
We use primary cultures of human tendon cells from both tendinopathy patients and healthy volunteers. (controls). The tendon cells are characterized using several contemporary methods of analysis on protein- and mRNA-level. The endogenous production of different biochemical mediators are measured and compared between the groups. The cultures are furthermore exposed to exogenously administered signal substances in different concentrations, and then different outcomes in terms of proliferation, apoptosis, receptor expression, and endogenous production of biochemical mediators are analyzed. In addition we use the experimental animal model for Achilles tendon overuse [6], which is based on a previous model by Backman and collaborators [7].

RESULTS
These studies are in their initial phases. Results so far confirm that several of the signal substances of interest may be proliferative to human tendon cells in a dose-dependent manner. However, in concentrations higher than the expected endogenous levels in healthy tissues, the substances seem to be cytotoxic. Furthermore, the endogenous production of the biochemical mediators by the tendon cells seems preserved in the \textit{in vitro} environment, and in fact, this production seem to be up-regulated after cyclic mechanical loading both \textit{in vitro} and \textit{in vivo}.

DISCUSSION
During the last years, increasing attention has been devoted to the biochemical milieu of human tendons. Although further experiments testing the functional importance of locally produced (non-neuronal) biochemical mediators in tendinopathy/tendinosis are needed, the present studies seem to provide evidence, already in the initial stages of experimenting, that the dramatic metamorphosis in local cell signalling reported for human tendinopathy tendons \textit{in vivo}, might be a driving factor for the tendinosis changes, such as cell proliferation. The theories of biochemical aspects of tendinopathy that have emerged might complement, rather than replace, existing hypotheses on the pathogenesis. They furthermore fit a theoretical model in which tendon pathology exists on a continuum that, at various points, involves abnormalities in blood vessels, nerves, tenocytes, and extracellular matrix [8].

REFERENCES

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The typical patient has a gradual onset of tendon pain, has morning stiffness and has had pain during tendon loading activities for more than 3 months (chronic). Traditionally these patients have been treated with rest, NSAIDs and pain-free exercises, most often with poor clinical results. Despite that biopsies already 30-40 years ago showed an absence of inflammatory cells in the tendon, anti-inflammatory treatment with NSAIDs and cortisone injections are being used. The traditional treatment is often focused to the inside of the tendon, injections of cortisone, PRP, autologous blood, or surgery using excision of “abnormal” tendon tissue or multiple longitudinal tendon incisions.

Because of the long recovery and unreliable and relatively poor clinical results after intra-tendinous surgical treatment, about 15 years ago we started to perform research on the chronic painful Achilles tendon at the Sports Medicine Unit in Umeå. First, instead of surgery, we subjected the chronic painful Achilles tendons to painful eccentric training. This was opposite to the generally accepted methods with pain-free rehabilitation exercises. Interestingly, the painful training caused a worsening the first week, but then there was a gradual improvement, and after 3 months with daily painful training there was a good clinical result in a high proportion of recreationally active and non active patients with midportion Achilles tendinosis.

Based on new findings using ultrasound and Doppler, and immunohistochemical analyses of tendon biopsies, the region with high blood flow and nerves outside the deep side of the chronic painful tendinosis tendon, but not normal pain-free tendon, was of high interest for new clinical studies. Local anaesthesia in the region with high blood flow and nerves outside the deep side of the tendon temporarily cured the pain, and this started studies on new treatment approaches. First, ultrasound+Doppler-guided injections of the sclerosing substance polidocanol, and later mini-surgical scraping in local anaesthesia, both methods targeting the region with high blood flow (and nerves), were tried in clinical studies. Sclerosing injections showed good results especially for the Achilles midportion, however, 2-3 injections with 6-8 weeks in between were needed to cure the pain during tendon loading activity. Mini-surgical scraping also showed good clinical results. This method is more radical compared to sclerosing injections, is a one-stage procedure followed by immediate weight bearing rehabilitation (3-6 weeks before full tendon loading sport activity), and consequently saves time for the patients. It seems that the more radical interference on the deep side of the tendon was related to a quicker cure of the tendon pain. Two to three year follow-ups of large patient groups have shown continued good clinical results with pain-free tendon loading activity.

After successful treatment with eccentric training, sclerosing injections or surgical scraping, blood flow has been normalized, the tendon thickness has decreased and the tendon structure has improved. Altogether, my clinical experience is that interference in the region with high blood flow and nerves outside the deep side of the chronic painful Achilles and patellar tendon, is associated with pain relief/cure in a majority of the patients. Tendon pain seems to be related to blood flow and tendon thickness/structure, that “normalizes” when the pain is cured. The soft tissues on the deep side of the tendon appears to be very potent, and of significant importance for the tendon.

All groups of patients, from non active over weight individuals to international top level athletes seem to benefit from the mini-surgical scraping procedure. We find now indications to “go inside” the tendon to treat chronic painful Achilles and patellar tendinosis.
No human is without the experience of pain, unless suffering from congenital indifference to pain. Yet, we have so far had difficulties establishing a unified concept of pain.

It is well known that many leading concepts of modern neuroscience find their origin in the inspiration by ancient Greek philosophers and medical thinkers. The conception of a human brain represents their greatest achievement, even though the controversy between cardiocentrists and encephalocentrists was still alive at the beginning of the modern scientific era. As suggested by the latter frontrunners, the human brain was not only the seat of intelligence, sensory perception and motor control, but also of emotions, pleasure and pain.

Not unexpectedly, our present definition of pain reads: “An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”. It is also stated that experiences described the same way, in the absence of tissue damage, should be accepted as pain as well. Taken together, pain is considered a psychological state that can include subjective conditions ranging from mere unpleasantness to extreme physical agony, or to the feeling of sadness and misery accompanying an episode of major depression. No wonder, speculations about the organization of a neuronal control system, known as “The pain system”, revealing such varied features continues to challenge the biological sciences. In fact, the concept of pain as a unique and separate sensation has been appreciated only within the past half century.

However, over the past four decades we have seen a true explosion of basic and clinical experimental studies aimed at understanding the mechanisms of nociception and pain. This has led to our broaden awareness of not only the refined neurobiology of nociceptors and their afferents, of projection neurons and ascending pathways, but also of the forceful and dynamic regulatory systems acting within the central nervous system. We have reached a point where an interpretation in agreement with neither a strict specificity model (“specificity theory”) nor a pattern model (“pattern theory”) of pain can account for all that has been established. Rather, it appears that different forms of pain such as nociceptive, inflammatory or neuropathic pains are mediated by a range of mechanisms. Presently, we believe that there are indeed specific nociceptive pathways, but these are subject to detailed facilitating and inhibitory controls as a result of changes in the properties of neurons in the central nervous system. Thus, pain is not merely a reflection of peripheral inputs or pathology but also a dynamic manifestation of central neuronal plasticity that is most probably a major contributor to many clinical pain conditions.

The presentation will focus on some old and some new issues on our still unfinished saga of “The pain system” relating to:

- The concepts of nociceptive, inflammatory, neuropathic pain and persistent /long-term (“chronic”) pain
- The impact of “The gate control theory” on the development of studies of nociception and pain
- The neurobiology of the nociceptors
- The spinal / medullary dorsal horn
- The nociceptive ascending pathways
- The cortical processing of nociceptive stimuli
- The descending modulatory systems
Long-term pain due to inflammation or nerve injury is a major health problem and is often worsened due to central sensitisation. The mechanisms behind these phenomena, and how the neuronal activity evoked by painful inflammation is processed by the nervous system, are not completely understood. Such responses are thought to result in part from central neuroimmune activation where glial cells may be key actors. In vivo, and in humans, pro-inflammatory cytokines exert pro-algetic actions, and when the glial production of pro-inflammatory cytokines is inhibited this response is blocked. Astrocyte networks detect changes in the CNS microenvironment and regulate brain activities under various physiological and pathophysiological conditions. One signalling pathway in this system propagates Ca\textsuperscript{2+} waves. The Ca\textsuperscript{2+} signalling over long distances is analogous to, but much slower than the propagation of action potentials in neurons. The astrocytic propagating Ca\textsuperscript{2+} waves can be evoked by transmitters released from neurons and glial cells followed by activation of especially G protein-coupled receptors. Cytosolic Ca\textsuperscript{2+} plays a key role as a second messenger and the control of Ca\textsuperscript{2+} signals is therefore critical. It depends upon the coordination of Ca\textsuperscript{2+} entry across the plasma membrane (PM), Ca\textsuperscript{2+} release from the endoplasmatic reticulum (ER), refilling of the ER stores, and extrusion across the PM. The Na\textsuperscript{+}/Ca\textsuperscript{2+} exchanger, a Ca\textsuperscript{2+} transporter that controls the intracellular Ca\textsuperscript{2+} concentrations, is driven by the Na\textsuperscript{+} electrochemical gradient across the PM, and this Na\textsuperscript{+} pump, Na\textsuperscript{+}/K\textsuperscript{+}-ATPase, indirectly modulates Ca\textsuperscript{2+} signalling. Inflammatory stimuli can disturb the astrocytic Ca\textsuperscript{2+} signalling, which results in downregulation of Na\textsuperscript{+} transporters, Na\textsuperscript{+}/K\textsuperscript{+}-ATPase, increased activity of inflammatory receptors, toll-like receptor 4 (TLR4), interleukin-1 receptor (IL-1R) and N-methyl-D-aspartic acid (NMDA) receptor, and increased release of proinflammatory cytokines, interleukin-1beta (IL-1\(\beta\)) and tumour necrosis factor-alpha (TNF-\(\alpha\)) from astrocytes and microglia. The involvement of the cytoskeleton in this organization controlling the PM microdomains and the ER complex seems to be of importance. An intact cytoskeleton is required for the propagation of astrocytic Ca\textsuperscript{2+} waves and disruption abolishes the Ca\textsuperscript{2+} oscillations by changing the balance between the Ca\textsuperscript{2+} regulating processes.

Novel treatment strategies for long-term pain to attenuate the neuroinflammation would be to restore the disturbed astrocytic Ca\textsuperscript{2+} signalling by modulating the Na\textsuperscript{+}/K\textsuperscript{+}-ATPase activity, and restrain the activity of inflammatory receptors. Thereby release of proinflammatory cytokines will decrease. This will be an important knowledge for treatment in clinical therapy.
Current pharmacological treatment strategies for pain associated with tendinopathies are restricted to the use of non-steroidal anti-inflammatory drugs and locally injected corticosteroids, the usefulness of which is debatable. There is a clear need for novel analgesic approaches. However, such analgesics need to be easy to administer, should not have central nervous depressant effects, and should not produce tolerance or dependence. Studies of image-guided injections of the local anaesthetic agent bupivacaine (+ hydrocortisone) and of the sclerosing agent polidocanol indicate that it is possible effectively to alleviate the pain at the peripheral level alone. In addition, the evidence for a sensory nervous involvement in tendinopathies suggest that orally active compounds that are analgesic in other persistent pain modalities may be useful here. Three possible targets will be discussed in this presentation:

- **TRPV1 receptor antagonists.** Transient receptor potential (vanilloid 1), TRPV1, are expressed on sensory neurons, and their activation by heat and low pH leads to the release of sensory neuropeptides. Capsaicin, found in spicy peppers, is a potent TRPV1 activator. Prolonged activation of the receptors with capsaicin can cause a desensitisation of the sensory signalling, and this compound is used clinically for the local treatment of postherpetic hyperalgesia. TRPV1 antagonists have proven active in a number of different pain modalities, and leading compounds are now in clinical trial. However, early data indicating off-target hyperthermia responses to TRPV1 antagonists may be a hurdle to their development.

- **Nav1.7 blockers.** Local anaesthetics exert their action upon voltage-sensitive sodium channels. Molecular biological techniques have identified at least nine different channels of the Nav1 class, and Nav1.7 has attracted considerable interest not only due to its selective localisation on sensory nerves, but also to the findings that mutations of this channel in man are associated with different sensitivities to pain. Nav1.7 blockers are currently under preclinical development.

- **Endocannabinoid-modulating agents.** Cannabis is used in some countries for the treatment of pain associated with Multiple Sclerosis, but its use is controversial, given its psychotropic properties. Δ9-Tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis, produces its effects via activation of cannabinoid (CB) receptors, and antinociceptive effects of CB1 receptor agonists have central, spinal and peripheral components. Peripherally-restricted CB receptor agonists are currently being investigated, but a more intensive area of research is the development of drugs focussing upon the enzymes metabolising the endogenous cannabinoids anandamide and 2-arachidonoylglycerol, since endocannabinoids are produced locally “upon demand”. Inhibitors of anandamide metabolism are active in a number of animal models of pain, but do not produce the psychotropic effects seen with THC.
SHOULDER IMPINGEMENT SYNDROME; EVIDENCE THAT CENTRAL SENSITISATION OF PAIN PROCESSING INFLUENCES CLINICAL PRESENTATION AND OUTCOME FOLLOWING SURGERY

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PURPOSE OF THE STUDY
To quantify the presence, and influence on outcome, of neuropathic-like symptoms in patients undergoing subacromial decompression for shoulder impingement

METHODS
Twenty patients with unilateral impingement syndrome of the shoulder, and awaiting arthroscopic sub-acromial decompression, were recruited. Twenty age and sex matched control subjects were also recruited. All control subjects were free from musculoskeletal pain.

All subjects underwent quantitative sensory testing of their right thenar eminence and over both shoulder. Subjects also completed Oxford Shoulder Scores and PainDETECT questionnaires that quantifies neuropathic elements of pain. Patients were also asked to complete updated questionnaires 3 months after their sub-acromial decompression.

RESULTS
Pre-operatively 14 patients reported referred pain radiating down the arm while 6 patients denied referred pain. The presence of referred pain pre-operatively resulted in a significantly worse outcome from sub-acromial decompression 3 months after surgery (unpaired t-test, P=0.035). Patients were also found to have significant hyperalgesia to punctate stimulus of the skin compared to controls (unpaired t-test, P <0.0001).

DISCUSSION
This work has identified that the presence of referred pain pre-operatively results in a significantly worse outcome than if referred pain is not present. This observation, together with the finding of varying levels of mechanical hyperalgesia in patients, are the first indicators of heterogeneity within patients presenting with shoulder impingement syndrome. These observations confirm the presence of central sensitisation in patients with impingement which may form a link between tendon nociception and pain perception.
INTRODUCTION

This study describes the prevalence of pain, functional loss and rotator cuff tears (RCTs) in a general population cohort.

METHODS

The Chingford cohort is a 19-year old longitudinal population study comprising 1003 women aged between 44 and 67 at baseline. To date 183 consecutive subjects (366) shoulders have been interviewed about their shoulders. Myometric strength assessment and high-definition ultrasound examination (US) have been performed on all shoulders. Additionally pain thresholds and perceptions of pain have been tested using quantitative sensory testing (QST) and a number of validated questionnaires, including the illness attitudes scale and the pain detect score.

RESULTS

The population prevalence of at least one full-thickness RCT was 24%, with 19% being unilateral and 5% bilateral.

The distribution of symptoms across the 366 shoulders is shown in table 1.

<table>
<thead>
<tr>
<th>Number (N)</th>
<th>Normal tendon (on US)</th>
<th>Abnormal tendon-bone interfaces</th>
<th>Partial-thickness tears</th>
<th>Full-thickness tears (≤2cm)</th>
<th>Full-thickness tears (&gt;2cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulders</td>
<td>206 (56%)</td>
<td>73 (20%)</td>
<td>34 (9%)</td>
<td>24 (7%)</td>
<td>29 (8%)</td>
</tr>
<tr>
<td>Pain</td>
<td>47 (23%)</td>
<td>26 (36%)</td>
<td>10 (29%)</td>
<td>7 (29%)</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>Functional loss</td>
<td>49 (24%)</td>
<td>26 (36%)</td>
<td>13 (38%)</td>
<td>7 (29%)</td>
<td>14 (48%)</td>
</tr>
<tr>
<td>Pain and functional loss</td>
<td>32 (16%)</td>
<td>20 (28%)</td>
<td>7 (21%)</td>
<td>4 (17%)</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>138 (68%)</td>
<td>40 (56%)</td>
<td>18 (53%)</td>
<td>14 (58%)</td>
<td>11 (38%)</td>
</tr>
</tbody>
</table>

Table 1: Distribution of symptoms across the different stages of tendon pathology

The pain and functional loss was significantly greater in the abnormal tendon-bone attachment group, and the full-thickness RCT (greater than 2cm) group, compared to those with no abnormality on high-definition ultrasound examination.

Strength testing showed progressive weakness through all disease stages.

Pain thresholds from the QST data will be presented.

DISCUSSION

In a unique normal population-cohort study significant pain and/or loss of function was found in 48% of shoulders with high-definition US abnormalities of the tendon. High-definition US has allowed us to identify a group of tendons with an abnormality at the tendon bone interface. The pain and functional loss increases at this stage and then only further increases once a tear is greater than 2cm. However over 50% remain asymptomatic.
PATELLAR TENDINOPATHY – GOOD CLINICAL RESULTS AND NEW FINDINGS WITH ULTRASOUND AND DOPPLER-GUIDED ARTHROSCOPIC SHAVING

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INTRODUCTION
Patellar tendinopathy/Jumper’s knee is known to be a troublesome condition to treat, and the diagnosis is not always easy. Maybe it is even more difficult than we formerly thought? In one of our studies we have used MRI, ultrasound (US)+colour Doppler (CD), and arthroscopy for evaluation and treatment.

METHODS
We are currently using a new treatment method for Jumper’s knee, US and CD-guided arthroscopic shaving (in local anaesthesia), that allows for an intra-articular evaluation of the knee joint. With this method we use the US to guide us to be precise in addressing the surgical treatment to the region with pathological changes and pain, without resecting anything of the tendon.

RESULTS
The clinical results after using this method are very promising, with athletes going back to sports within 6-8 weeks after treatment. This method allows for a fairly aggressive rehabilitation after surgery especially compared to former surgery with open tenotomy.

DISCUSSION
Interestingly, there are also other findings during the arthroscopic evaluation that is of clinical interest. Many of the patients with patellar tendinosis were despite a normal MRI pre-operatively found to have additional intra-articular pathology, such as; cartilage damage in the patello-femoral joint and large plicae formations. Does this knowledge influence the way we will diagnose and treat patellar tendinopathy patients in the future? Does this influence the results in former studies?

REFERENCES
EFFECTS ON THE CONTRALATERAL TENDON/MUSCLE WHEN THE LIMB ON ONE SIDE IS MARKEDLY OVERUSED – IMPLICATIONS FOR TISSUE CHANGES AND PAIN?

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INTRODUCTION

Bilateral affection of joints occurs for patients with rheumatoid arthritis (RA). The nervous system is considered to contribute to the inflammation in RA, which may explain why the joint affections occur bilaterally. The contralateral untrained limb can furthermore to some extent benefit from unilateral strength training (1). The nervous system may also here be involved (2). Cross-over effects via the spinal cord can occur and the peripheral innervations may be involved. However, the exact mechanisms for the cross-over effects are unclear. Experimentally, it is previously shown that unilateral injections of CGRP in the hindpaw leads to bilateral effects (3).

MATERIAL & METHODS

An experimental model is used in our laboratory for which the effects of marked overuse of the triceps surae muscle on one side are analyzed for. Repetitive passive flexion-extension of the ankle is achieved and during the flexion phase, an active contraction is furthermore achieved via electrical stimulation. Most importantly, not only the ipsilateral but also the contralateral limb (triceps surae muscle, Achilles tendon) are analyzed.

RESULTS

Tendinosis-like changes occur not only in the Achilles tendon of the overused leg but also contralaterally. This fact is an important part in a Thesis presented by Gustav Andersson. Morphological changes do also occur within muscle tissue on both sides. The changes were related to the occurrence of muscle fiber necrosis, internal nuclei and inflammation. There was a parallellity concerning the two sides in the achievement of the morphological changes when examining for the different time frames in the model. Furthermore, increased levels of the neuropeptide substance P within the muscle were found, a correlation being seen between the exercised and the non-exercised legs. These aspects concerning bilateral muscle affection will be highlighted by Yafeng Song (via a Poster). Besides these findings, bilateral observations concerning nerve fiber affections and S-100b expressions have been made.

DISCUSSION

The findings in our experimental model stress the fact that the contralateral leg, both concerning the Achilles tendon and the triceps surae muscle, should not be used as control structures when interpreting the results of the model. Contralateral effects were markedly seen. Neuronal mechanisms are likely to be involved. The considerations that contralateral strength improvements occurring after exercise may be related to neuronal adaptations (4) favour such an interpretation. From a clinical point of view it is of interest to note that 50% of patients with Achilles tendinosis have the symptoms bilaterally and that unilateral treatment often leads to effects bilaterally. Up-coming studies using the experimental model will further clarify the mechanisms for the occurrence of bilaterality in response to marked overuse of muscle/tendon.

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KEY NOTE LECTURE 1, SESSION III:

COMPRESSSION AND TENDINOPATHY

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Tendon is biologically active and responsive to change in mechanical load. Traditionally, tendons are thought to withstand only tensile loads. However, compression load on tendons is common and can change tendon morphology towards fibrocartilage. Interestingly, tendon pathology appears to have fibrocartilaginous parallels, even in tendons where tensile loads predominate, such as the mid Achilles. The combination of compressive and tensile load may be more detrimental to tendons than one type of load.

Clinically, tendinopathy at the insertion appears to affect both the insertion of tendon into bone as well as at the fulcrum prior to insertion. Individual morphology may be an important aetiology in predisposing an athlete to tendinopathy. Compression plays a key role in pathological change at the fulcrum, whereas true insertional tendinopathy may lack a known compressive aetiology. Treatment of these tendons should vary to account for the loading profiles. Even in non-insertional tendinopathy, compressive forces may have a role, both from internal and external sources. Further research to identify the role of compression in all tendinopathies will improve treatment options.
THE DEVELOPMENT OF AN ULTRASOUND-GUIDED CORE NEEDLE BIOPSY TECHNIQUE FOR SAMPLING ROTATOR CUFF TENDON

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INTRODUCTION

Basic science research into the mechanisms behind the onset and progression of rotator cuff pathology are poorly understood due to the lack of access to tendon tissue across the spectrum of disease. Existing work has been restricted to analysis of tissue collected from cadaveric specimens and from rotator cuff repair surgery. Invariably this represents tendon tissue that has progressed to the later stages of damage and degeneration. Lack of tissue analysis from rotator cuff tendons showing clinical signs of early disease, such as tendinopathy in the absence of a tear, has led to a gap in our understanding of the aetiology of this condition.

The effects of current therapies for rotator cuff pathology on the biology of the target tissues are poorly understood and, as such, explanation of the mechanisms of their relative efficacy or potential damage is not possible. Analysis of tissue would permit further investigation into these unanswered questions and offer the opportunity to develop a more informed pursuit of future therapies.

The aims of this study were to develop a minimally invasive, ultrasound-guided core needle biopsy technique for sampling rotator cuff tendon that could be used for pre and post treatment analysis and for longitudinal study of disease natural history.

METHODS

A number of biopsy needles used for sampling soft tissues were evaluated for quality and consistency of tissue sampling, ease of use and cost. They were initially tested using cadaveric sheep shoulders and ultrasound phantom models. The quality and consistency of samples was evaluated at the time of biopsy and confirmed with histology until the selection was refined to two possible needles. The two needles were then used to sample human rotator cuff tendon intraoperatively during shoulder surgery. Samples were processed and evaluated for adequacy using light microscopy.

The optimum needle was then used to obtain biopsies of rotator cuff tendon from patients with clinical signs of pathology in a clinic setting. The procedure was performed under local anaesthetic, aseptic conditions and ultrasound guidance.

RESULTS

Two needles were selected: a BARD Magnum™ reusable biopsy device with disposable 14G needles and a Temno Evolution™ 14G disposable needle. Both needles gave reliable and consistent tissue samples from cadaveric sheep and ultrasound phantom models. Intraoperative testing found the BARD Magnum™ device to be more consistent than the Temno Evolution device™ in delivering high quality core tissue samples. Histological analysis of both sheep and human samples compared favourably with routine tissue resections taken from around the biopsy site.

Biopsies performed in a clinic setting underwent an iterative process of improvement in patient positioning, needle entry point and local anaesthetic technique to optimise the procedure. The final iteration used 10ml 1% lidocaine infiltrated into the subacromial bursa and the planned needle track for biopsy. Patients tolerated the biopsy technique well and follow up of the first fifteen participants at around seven weeks did not reveal any tendon changes visible on ultrasound evaluation.

DISCUSSION

We have described a novel technique for accessing tissue samples from the rotator cuff in a clinic setting that are suitable for histological analysis. This method offers the opportunity to study the aetiology and progression of rotator cuff disease in addition to evaluation of current and future therapies at a tissue level. This procedure presents clinical researchers with a tool that may lead to identification of tissue biomarkers relevant to the progression and treatment of rotator cuff disease.

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CONTRAST ENHANCED ULTRASOUND EVALUATION OF THE ROTATOR CUFF

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INTRODUCTION
Ultrasound assessment of the rotator cuff is currently focused on evaluating the structural integrity of the tendons with little ability to measure the biological condition of the tissue. Contrast enhanced ultrasound uses an intravenous gas microbubble agent to provide a quantifiable measure of blood volume and flow within a tissue. The microbubbles are comparable in size and behaviour to human red blood cells. These gas-filled structures are highly compressible by ultrasound waves and offer the potential to quantify the contrast and, hence, blood content within a region of contrast perfused tissue by delivering modified ultrasound wave patterns to the target tissue. The aim of this study was to investigate if such a technique could be used to develop an image-based biomarker of rotator cuff disease.

METHODS
Investigations were carried out on patients having shoulder surgery under general anaesthetic and in patients with clinical features of rotator cuff pathology in a clinic setting. The ultrasound machine used was a Logiq E9™ (GE Healthcare) with a 9L-D linear array transducer. The investigations were performed using a 5ml intravenous bolus of the third generation ultrasound contrast agent SonoVue™ (Bracco, Italy). The machine was set use a 4.5MHz contrast-specific mode and iterative adjustments to the ultrasound power (affecting mechanical index) were made across participants to optimise the machine settings. A three-minute video loop was recorded from the moment of bolus injection.

Offline analysis of the video loops was undertaken and time-intensity curves generated for regions of interest within the rotator cuff tendons and a control region within a peri-bursal arterial vessel.

RESULTS
Twenty-one participants (aged 34–77 years, 14 male) underwent contrast enhanced ultrasound evaluation of the shoulder. Ten of the participants had the investigation performed under anaesthetic and eleven were completed in a clinic setting; both groups showed similar results. All contrast studies resulted in typical time-intensity curves for the control areas of the image. Intratendinous regions of interest did not show any change in ultrasound intensity above noise level in response to the contrast administered at a range of ultrasound power settings (mechanical index 0.13-0.4).

DISCUSSION
In this study we aimed to optimise a contrast enhanced ultrasound technique to develop a quantifiable measure of blood volume within rotator cuff tendon as a biomarker of tissue condition. The results of the study show that, although the technique worked well across all machine settings, patient variations and anaesthetised versus awake patients for the arterial control region of the images evaluated, the blood volume present within rotator cuff tendon was not sufficient to be detected using this imaging method.

The ability to detect the presence of contrast within a tissue is dependent upon the concentration/volume of blood present within a region of interest and the sensitivity and resolution of the ultrasound equipment used. We aimed to use the most sensitive methods available for this study and found that this technique is not suitable for evaluating microvasculature with the rotator cuff tendons.

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Figure 1. Time intensity curves for control (arterial) and intratendinous regions of interest (ROI)
ULTRASOUND GUIDED TENOTOMY OF GLUTEUS MEDIUS TENDINOPATHY (GTPS):
A DIFFICULT TOPIC TO TREAT

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INTRODUCTION
The greater trochanter pain syndrome (GTPS) is a painful condition that must be well-studied before doing any therapeutic intervention. Clinical examination supported by ultrasound (U.S) and MRI are the two best imaging options for studying this painful condition. It has already been described a few years ago by different authors in the lateral elbow and patellar tendon, the possibility of ultrasound guided percutaneous tenotomy technique for these tendinopathies.

We report a case of a 75 years old woman who went under this technique applied to gluteus medius tendinopathy after six months of painful situation in this area.

METHODS
We assumed the possibility of reproducing the U.S guided percutaneous tenotomy applied to gluteus medius tendinopathy under neuroleptoanalgesia of the patient in order to be a painless procedure.

Approaching the target from proximal to distal (U.S guided longitudinal view - two hands technique) with a 18-gauge spine needle fixed to a 10 ml syringe filled with 2% Lidocaine, we oriented the point of the needle inside the tendon trying to reach first the osteophytes and doing multiples fenestrations inside the tendon and in the bony surface of osteophytes and inside the calcifications.

After doing it we deposited 30 mg of Triamcinolone + 3 ml Bupivacaine 0,5% on the surface of gluteus medius tendon and under tensor fascia lata. We recommended criotherapy 5 times a day for 5 days in 15-20 minutes per session after the intervention.

RESULTS
After 4 weeks of the intervention the patient referred totally disappeared of the pain on lateral side of the thigh and groin with no important side effects, nevertheless she still reported low back pain and irradiation to posterior thigh of the same leg, why she was studied for a concomitant low back pain origin.

DISCUSSION
Sometimes is difficult to discern the etiology of trocanteric and peritrocanteric pain conditions but clinical examination alongside ultrasound and/or MRI of this and lumbar area should be the first studies to take decisions about any kind of treatment. This condition is so called the rotator cuff tendinopathy of the hip.

If we have patients with pain on trocanteric or peritrocanteric area and data of gluteal tendinopathy on insertion in mayor trochanter in terms of calcifications, entesophytes, hipoecogénic and increased size tendon or anecogenic area inside the tendon (by U.S) or increased signal intensity of tendon, distension of subgluteus bursa or attenuation or thinning of tendon in case of partial or total ruptures of tendons (by MRI), we should consider the option of ultrasound guided percutaneus tenotomy in order to promote the healing of that tendon or at least to do an infiltration on the surface of the tendon as a test for studying the pain origin.

REFERENCES

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CLINICAL EVALUATION OF ULTRASOUND-GUIDED PERCUTANEOUS LAVAGE AS A TREATMENT OPTION FOR CALCIFYING TENDINOPATHY OF THE SHOULDER

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INTRODUCTION
Calcifying tendinopathy of the rotator cuff is a frequent shoulder complaint of unknown origin. It may present as asymptomatic and can be seen in athletes. Various treatments options have been tried in an endeavor to dissolve the calcification, these include: infiltration, shockwaves and arthroscopy. The aim of this study was to conduct a clinical assessment of the use of ultrasound-guided percutaneous lavage as a treatment for calcifying tendinopathy. The study design is a Case series study.

METHODS
Fluoroscopy and ultrasound-guided assessment was performed in 88 patients to evaluate the presence or absence of pain before and following lavage of the rotator cuff to eliminate calcification.

RESULTS
The majority patients were women (65.9%) and the mean age was 45 years old. The complaint most often presented was in right shoulder, the most often affected (54.5%) affecting the supraspinatous tendon (87.50%). In 87.30% of the cases by means of lavage it was possible to extract calcified material using a syringe. There are statistically significant differences in the affected tendon regards presence of absence of pain at 15 days post procedure (p<0.001). At six months 97.7% of the patients felt no pain, although on the ultrasound images of 25 patients there was some sonic shadow (p<0.023). By 9 months 98.9% of the patients had neither pain nor shadow on their ultrasound images with a p value of p<0.001).

DISCUSSION
Ultrasound-guided percutaneous lavage is an effective technique which can be performed in an outpatient setting, it is easy to perform and has minimal side effects.
EVALUATION OF CONSERVATIVE TREATMENT PROGRAM OF PARTIAL TEARS OF ACHILLES TENDONS BASED ON NEW SONOGRAPHIC CHANGES OF PARTIAL TEARS: A PILOT STUDY

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INTRODUCTION
A recent study has proposed new sonographic changes to diagnose partial midportion achilles tendon ruptures 1. Treatment of partial tears of Achilles tendons has not been adequately defined in the literature. This study evaluates a conservative treatment program for partial tears of Achilles tendons diagnosed by power Doppler ultrasound.

METHODS
Twenty-eight subjects (25 men and 3 women) with a mean age of 45.5 years (range 23-81) with Achilles tendon pain and evidence of a partial tear on power doppler ultrasound were recruited over one year. Twenty-five subjects were managed conservatively with heel lifts and cross training for 3 months. Three subjects required immediate surgery because of gross changes.

RESULTS
Twenty-four out of the twenty-five subjects treated conservatively were able to return to their usual sporting activity (p< 0.05) and demonstrated improved VAS scores after 3 months (p<0.05) which persisted after 1 year (p<0.05). In addition, repeat power Doppler ultrasound after 3 months demonstrated improved collagen arrangement and resolution of the abnormal blood flow in all cases. One subject treated conservatively did not show improvement in VAS scores or power doppler ultrasound findings and required surgery after 3 months. This case had had previous multiple intra-tendinous injections.

CONCLUSION
Conservative treatment of partial tears of Achilles tendons with heel raises is successful in managing the majority of subjects who present with Achilles tendon pain and sonographic changes of a partial tear. Further studies are required to investigate the usefulness of this treatment program including the reasons for failures.

REFERENCES
THE EFFECT OF A MILITARY TRAINING ON THE VASCULAR RESPONSE OF THE ACHILLES TENDON
A PROSPECTIVE DESIGN IN MILITARY RECRUITS

Mahieu NN (1), Van Tiggelen D (1,2), De Muynck M (3), Dumalin M (4), and Witvrouw E (1)

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INTRODUCTION
A reactive tendinopathy is a non-inflammatory proliferative response in the cell and the matrix, which occurs with acute tensile or compressive overload [1]. It has been shown in a previous study, that a military training can elicit a reactive tendinopathy in 14.5% of the military recruits [2]. The purpose of this study was to investigate the link between the pain in reactive tendinopathies and their intratendinous Doppler activity.

METHODS
The vascular response of the Achilles tendon was evaluated during a military training program of six weeks. Forty-nine male military recruits (98 tendons) volunteered for this study. Before and during the military training program, the Achilles tendons were screened with gray-scale ultrasonography and power Doppler US. Reactive tendinopathies of the Achilles tendons were registered by means of a clinical examination, VAS-scores and VISA-A scores.

RESULTS
The US examination, the clinical examination, VAS – scores and VISA – A scores showed that 13/98 tendons developed a reactive tendinopathy. Only three of these 13 symptomatic tendons showed intratendinous Doppler activity. In these tendons, pain was always present before the vascular response of the Achilles tendon. Both pain and hypervascularisation remained visible till the end of the basic military training. In five asymptomatic tendons with no structural changes of the tendon, a vascular response was seen during one single assessment.

DISCUSSION
To our knowledge, this is the first prospective study that looked at the development of hypervascularisation in a specified subpopulation, i.e. reactive tendinopathy. It can be concluded that there is no relationship between the vascular response of the Achilles tendon and the pain in a reactive tendinopathy. In a reactive tendinopathy, other pain mechanisms must be investigated in future research. It is possible that the obscurity about the role of the vascular response in the pain mechanism of a tendinopathy may be explained to some extent by the different stages of tendinopathy.

REFERENCES

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Our understanding of the cellular basis to the tipping point between load adaptation and early reactive tendinopathy in athletes is quite limited. This presentation will explore the concepts around a possible role of connexions in early reactive tendinopathy. Connexins can elicit either an excitatory or an inhibitory response within the matrix and are a part of the non-neural pathways utilised in intratendinous signalling. The lecture will examine present knowledge about tendon response to repetitive load, tenocyte response to compression, and factors relating to aggrecan expression and breakdown. The clinical presentation of reactive tendinopathy may be explained by mechanically mediated and cell driven processes. Even though tendon response to stress is multifaceted, changes in the normal cell-to-cell communication via connexins may explain tendon sensitivity to high loads. Further, treatment options for early loading of acute reactive tendinopathy based on these principles have demonstrated clinical promise.
DEVELOPMENT OF A MOLECULAR MARKER OF TENDON DISEASE - VALIDATION IN NATURALLY OCCURRING TENDON INJURY

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INTRODUCTION
Routine diagnostic imaging using ultrasonography has been the lynchpin for the diagnosis of tendon disease but recent epidemiological studies have confirmed that this imaging technique cannot be used for predicting injury in horses (Avella, Ely et al. 2009). Furthermore, there are injuries where ultrasonography has poor sensitivity, such as for the diagnosis of tendon tears within the digital sheath. In these situations, molecular markers detected in the blood or tendon sheath synovial fluid would provide an alternative approach for the prevention and diagnosis of tendon disease. When a tendon is damaged, there is both physical and enzymatic destruction of the extracellular matrix which releases proteins and protein fragments into adjacent synovial fluid when there is a surrounding tendon sheath and also into the blood and lymphatics. The best choices of protein biomarkers are those released into either the tendon sheath synovial fluid (for intra-thecal injuries) or minimally filtered by the lymphatics so that detectable amounts are released into the blood. Cartilage Oligomeric Matrix Protein (COMP) is one suitable protein as it is abundant in the extracellular matrix of tendon and released with injury. However, previous studies (Smith and Heinegard 2000) indicated that quantification of the total amounts of COMP in the blood did not reflect the presence of tendon disease in the horse, thought to be because of high normal levels in blood (~1ug/ml) and relatively low amounts released from tendon after injury. Therefore we have been developing a more sensitive assay based on neo-epitope technology where an antiserum-based assay only recognizes the cleaved portion of the protein released after injury.

MATERIALS AND METHODS
COMP fragments were partially purified using ion-exchange chromatography from synovial fluids from natural injury and media from tendon explants with and without stimulation by a C-terminal fragment of heparin (Johnson, Smith et al. 2004). Fragments that appeared to be unique to tendon and released in greatest amounts with injury were identified by Western blotting using anti-COMP antisera. The cleavage site was then identified using MALDI-TOF mass spectrometry using trypsin, chymotrypsin, endoproteinase Lys-C and Asp-N digestion of the cleaved COMP from SDS-PAGE separation of the cleaved proteins. These digest ‘maps’ were compared with the digestion of intact COMP to identify those with a new N-terminal sequence indicative of the cleavage site. The cleavage site was confirmed using tandem mass spectrometry. From the determined cleavage sequence, neo-epitope antisera were generated. An 8 amino-acid peptide which matched the sequence of the N terminal side of the cleavage (representing the new N terminus of a COMP fragment released after injury) was synthesized and, bound to KLH then used to immunize a rabbit in conjunction with Freunds Adjuvant. This antisera was used with the synthesized peptide to develop an inhibition ELISA which was used to quantify levels of COMP fragment in synovial fluids obtained from normal (uninjured horses; n=5) and those with arthroscopically detected intra-thecal tendon pathology (n=13).

RESULTS
A ~100kDa fragment was identified in septic and inflammatory synovial fluids from digital sheaths and in the media from explants stimulated with the fibronectin fragment. This band was used for subsequent analysis with mass spectrometry and neo-epitope antisera generation. Normal digital sheath synovial fluid contained on average 5.28 µg/ml ± 1.33 (sd) of COMP neo-epitope. In contrast horses with intra-synovial tendon injuries had average COMP neo-epitope levels of more than 10 times the normal level (55.12 µg/ml ± 64.32 (sd); see Figure 1; p=0.011). Joint synovial fluid from normal joints and those with an OCD lesion did not show any significant differences between conditions, nor from normal digital sheath synovial fluid.

CONCLUSION
The development of this neo-epitope antiserum shows considerable promise as a sensitive and specific indicator of tendon pathology in synovial fluid. It will now be necessary to test this assay in blood samples in horses with intra-thecal and extra-thecal tendon disease.

REFERENCES
INTRODUCTION
Regenerative medicine offers the prospect of restoring normal, or as close to normal, structure and function to an injured organ and thereby resulting in a successful restoration of activity without the risk of re-injury. Over-strain and traumatic tendon and ligament injuries are common in the horse and, for the most part, heal (repair) naturally by the formation of scar tissue. However the scar tissue formed in this repair is functionally deficient compared to normal tendon, which has important consequences for the animal in terms of reduced performance and a substantial risk of re-injury, in spite of a multitude of treatments that have been proposed. As pain is not usually a feature of these conditions in the long-term, the primary need is to restore functionality and so this has encouraged the development of regenerative strategies. Mesenchymal progenitor, or stem, cells (MSCs) have been considered an ideal source of cells for regenerative medicine because it can be demonstrated, in horses as in other species, that they are capable of differentiating into different cell lines and synthesise new matrix (usually chondrogenesis, adipogenesis and osteogenesis). These cells are thought to be present in small numbers in most tissues but we have chosen to harness the action of MSCs recovered from bone marrow because of ease of recovery, minimal donor site morbidity, and, as these stem cells can be recovered from adult tissue, the possibility of autologous re-implantation which carries fewer regulatory and safety issues.

Equine digital flexor tendon strain injuries provide many of the elements required for tendon tissue engineering – the lesion manifests within the central core of the tissue thus providing a natural enclosure for implantation and, by the time of stem cell implantation, is filled with granulation tissue which acts in the role of a scaffold. It has the added advantage of being highly vascularised and therefore capable of nutritional support of the implanted progenitor cells. The cytokine and mechanical environment, which are potentially important drives for differentiation, is provided by the intra-tendinous location of the cells and the suspension of MSCs in bone marrow supernatant which has been shown to have significant anabolic effects \textit{in vitro}\textsuperscript{[1]}. We have hypothesised that the implantation of autologous MSCs, in far greater numbers than are present normally within tendon tissue, would have the potential of improving the repair of the tendon both structurally (by optimising mechanical properties, organisation and composition) and functionally (by reduced re-injury rates).

MATERIALS AND METHODS
Clinical data: Bone marrow was recovered from the sternum under standing sedation, generally within 1 month of injury, and transferred to a laboratory for culture and expansion of MSCs. After approximately 3 weeks, the cultured cells were transferred back to the veterinarian (10-50\times10^{6} cells, depending on the extent of the lesion) and implanted into the damaged tendon of the same horse under ultrasound guidance. After implantation, the horses underwent a week of box rest followed by a controlled exercise programme for up to 48 weeks.

Experimental study: 10 horses with naturally occurring SDFT injury were randomly allocated to treatment groups - 1\times10^{7} autologous bone marrow derived MSCs, obtained as described above) were implanted into the damaged SDFT of the treated group. Saline was injected into the control group. Horses received controlled exercise and were euthanased after 6 months. Non-destructive mechanical testing assessed structural stiffness of the SDFT and morphological and compositional analysis was performed on the tendon tissue.

RESULTS
Clinical data: To date in excess of 1500 horses have been treated worldwide with this technique. Analysis of clinical outcome in 113 treated UK National Hunt racehorses gave a re-injury rate of 25.7\% for those horses which had returned to full training and had been followed up for 2 years after treatment. This re-injury rate was significantly better than for the same type of horse treated conventionally and analysed in the same way (56\% re-injury rate for National Hunt horses; \textit{p}<0.05 \textsuperscript{[3]}). Histopathological examination has been carried out on 17 tendons from post mortem samples obtained from 12 horses which have undergone MPC implantation. These have shown both good quality healing with minimal inflammatory cells, and crimped organised collagen fibers. Furthermore, there was no evidence of any abnormal tissue or neoplastic transformation. In addition, labeled MPCs were detected in enclosed lesions for up to 4 months, similar to that described previously \textsuperscript{[4]}.

Experimental study: MPC-treated tendons exhibited normalisation of their mechanical, morphological and compositional parameters towards that of uninjured tendons. This was significantly different (\textit{p}<0.05) from saline treated tendons for cross-sectional area, cellularity, crimp pattern, and DNA content.

CONCLUSIONS
Treatment with MPCs appears to reduce re-injury rates in superficial digital flexor tendon injuries in National Hunt racehorses. This is supported by improvement in mechanical, morphological and compositional parameters in a controlled experimental study using naturally occurring disease.

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ACKNOWLEDGEMENTS
This work was performed in collaboration with VetCell Bioscience Ltd. of which RKWS is a Director.
INTRODUCTION

Achilles tendinopathy of the midportion is a typical overuse injury; various conservative treatments are commonly used; surgery is reserved for patients who do not respond adequately to conservative treatment.

The aim of this retrospective study was to assess the mid-term results of surgical treatment of chronic Achilles tendinopathy of the midportion and to analyse any difference in subjective and functional outcome in patients treated with longitudinal incisions and patients treated with fascial graft of gastrocnemius-soleus.

METHODS

From January 2004 through July 2009, 54 patients (45 men, 9 women) were surgically treated for Achilles tendinopathy of the middle third. The diagnosis was based on patient's history, clinical examination and ultrasound and/or MRI evaluation.

The mean age at the moment of surgery was 43.6 years (range 23-72) in the overall group. The follow up was at least 6 months.

Patients were divided in two subgroups according to their treatment: in Group A longitudinal incision were performed (24 patients), instead Group B had fascial graft of soleus (30 patients). To evaluate any difference in post-surgical outcome between the two groups, all the patients were interviewed about postoperative pain at rest, time to return to walk and to run without pain, thickening of the tendon, any further surgical procedure required and patient's satisfaction.

RESULTS

Pain at rest was absent 7 days after surgery in 83.3% of patients (87.5% in Group A, 80.0% in Group B). Return to walk was reach 6 weeks after surgery in 83.3% of patients (70.3% without pain); in Group A it was 87.5% and 75.0% respectively, in Group B 80.0% and 66.6%.

Return to run was reach within 4 months in 62.9% of patients, without pain in 42.6%. In the longitudinal incision group the results were 62.5% and 37.5% respectively, instead in the fascial graft of soleus group were 63.3% and 46.6%. Run without pain was obtained within 6 months in 75.0% of patients in Group A and in 80.0% of patients in Group B. Thickening of the tendon happened in 50.0% of patients in Group A and in 56.6% in group B.

Failure that needed surgical revision happened in 4 cases (7.4% of overall patients): 3 in Group A (12.5%), 1 in Group B (3.3%).

DISCUSSION

Surgical treatment of chronic Achilles tendinopathy gives good and acceptable mid-term results. The goal for the treatment is to return the patient to the desired level of physical activity without residual pain and with a recovery time as short as possible.

Longitudinal incisions of the tendon and fascial graft of soleus had comparable results in terms of pain at rest and thickening of tendon. Patients receiving fascial graft of soleus needed more time to walk without pain, probably due to haematoma in donor region, but had a faster return to run without pain and had a lower incidence of surgical revisions.

REFERENCES

INTRODUCTION

Heavy load eccentric training (ET) has been shown to be more effective than concentric training (CT) in treating Achilles tendinopathy.\(^1,2\) It is unclear at what speed ET should be performed to treat the condition with greatest efficacy. Recent studies have indicated that high frequency tendon force fluctuations may underpin therapeutic mechanotransduction, but the effect of training speed on resulting tendon vibration remains unexplored. The aim of this study was to compare tendon vibration during ET and CT at three speeds commonly employed during conservative treatment.

METHODS

24 healthy volunteers (12 male and 12 female, age = 27.8 ± 1.9 years) performed ET and CT exercises for the Achilles tendon either at a fast (loading phase = 1.5s), medium (loading phase = 3s) or slow pace (loading phase = 6s). Tendon vibration was measured by analysing the power spectra of the ground reaction force vector using a fast Fourier transform with 1Hz windows, and compared using ANOVA.

RESULTS

High frequency vibrations (8-13 Hz range) were greatest during fast and medium speed ET, with a mean of 15.8 N\(^2\)/Hz (sd = 8.8). This was significantly greater than all other combinations of conditions and speeds (p value range across these frequencies = 0.03 – 0.001). No significant differences between any combinations of speed and loading condition were found in the 1-7Hz low frequency range (p value range = 0.11 – 0.98).

CONCLUSION

The observed high frequency Achilles tendon force fluctuations during fast and medium speed ET were mostly in the higher frequency range, reflecting where physiological tremor particularly occurs. This may reflect inefficient recruitment of large motor units at high speeds, creating oscillation frequencies that are known to stimulate mechanotransduction in tenocytes. These findings were made in normal subjects and pave the way for exploration in patients with tendinopathic disease.

KEY WORDS

Loading, speed, frequency content

REFERENCES

INTRODUCTION
A relationship has been identified between vascularization on Doppler ultrasound (Doppler signal) and Achilles tendon pain. A Doppler signal is therefore an important clinical finding as it increases the likelihood that the tendon is painful. Doppler signal may be easier to detect several minutes after impact activity (Cook et al. 2005, Boesen et al. 2006). However, the immediate impact of activity on Doppler signal has not been investigated. The purpose of this study was to identify the relationship between activity and Achilles tendon Doppler signal among symptomatic tendons and asymptomatic controls.

METHODS
A case-control study was undertaken. Patients between the ages of 18-65 with Achilles tendinopathy were included. Criteria for Achilles tendinopathy were pain localised to the midportion of the tendon and abnormal gray-scale ultrasound imaging. Matched controls were recruited. Both groups performed two activity tasks: 1) a two minute step test; and, 2) repeated double leg calf raises for 1 minute. Activity tasks were separated by 30 minutes rest. Doppler ultrasound measurements were taken at rest and within 1 minute of completion of the activity tasks. Doppler signal was measured using a semi quantitative scale (Modified Ohberg Scale) and quantitively (pixel count from saved images).

RESULTS
A total of 10 symptomatic tendons from 7 cases (3 bilateral) were compared to 12 asymptomatic tendons from 6 controls. Symptomatic tendons had larger anteroposterior diameter than asymptomatic tendons (p<0.05). Doppler flow was present in 90% of symptomatic individuals and 0% of asymptomatic controls. Following both the repeated step up and repeated calf raise tasks, power doppler signal (number of pixels) decreased significantly (p<0.05). No flow was detected in the asymptomatic tendons before or after activity.

DISCUSSION
Doppler flow appears to decrease in patients with Achilles tendinopathy immediately following activity. When imaging patients immediately following activity it may be more difficult to detect Doppler signal in the Achilles tendon and this may have implications for diagnosis and management.

REFERENCES
PLATELET-RICH PLASMA TREATMENT IN CHRONIC ACHILLES TENDINOPATHY: A DOUBLE-BLIND RANDOMISED CONTROLLED TRIAL WITH ONE YEAR FOLLOW-UP

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INTRODUCTION

Chronic Achilles tendinopathy occurs frequently and is very hard to treat. The disease involves local degeneration of tendon tissue, of which regeneration may be improved by injecting platelet-rich plasma (PRP), an increasingly used therapy for releasing growth factors into degenerative tendon. However, high-quality randomised clinical trials on this topic are lacking. The aim of this study was to evaluate the effect of a PRP injection in patients with chronic Achilles tendinopathy.

METHODS

In this stratified, block randomised, double-blind, placebo-controlled trial at single center (MCH) 54 patients aged 18-70 years were randomised in two treatment groups. Next to an eccentric training program the patients received either a blinded injection containing platelet-rich plasma (PRP group) or saline (placebo group). As a primary outcome, the objective and validated Victorian Institute of Sports Assessment-Achilles (VISA-A) score was assessed and ultrasound examination performed at baseline and all follow-up appointments.

RESULTS

After randomisation into the PRP group (n=27) and the placebo group (n=27) there was a complete follow-up. After one year, the mean VISA-A score improved in both the PRP-group and the placebo group. There was no significant difference in increase between both groups (adjusted between-group difference, 5.5; 95% CI, -4.9 to 15.8, p=0.292). Ultrasonographic tendon structure improved significantly in both groups, but not significant different between both groups (adjusted between-group difference, 1.2 %, 95% CI, -4.1 to 6.6, p=0.647).

DISCUSSION

One-year follow-up analysis of the world’s first randomised controlled trial showed no evidence for the use of platelet-rich plasma injection in chronic Achilles tendinopathy. These findings are in line with our 6 months results [1].

REFERENCES

ALTERED PROTEOGLYCAN METABOLISM IS A FEATURE OF HUMAN PATELLAR TENDINOPATHY

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INTRODUCTION
Overuse patellar tendinopathy is common in individuals participating in exercise and sport and is characterised by proximal patellar tendon pain and tenderness. Studies have shown that a predominant feature of tendinopathy is a change in the organization of the extracellular matrix and we have shown that in human patellar tendinopathy there are increased amounts of the large aggregating proteoglycans, aggrecan and versican in the extracellular matrix compared to normal tissue (1). The aim of this work was to investigate the differences in the metabolism of proteoglycans between patellar tendon exhibiting chronic overuse tendinopathy and normal patellar tendons in humans.

METHODS
Rates of synthesis and catabolism of proteoglycans were determined by incubating normal (n=9) and pathologic (n=12) samples of human patellar tendon with [35S]sulphate and determining the rate of incorporation of [35S]sulphate into proteoglycans and the rate of loss of 35S-labelled proteoglycans with time in explant culture. The radiolabelled and total proteoglycans retained in the tissue and lost to the medium were analysed by fluorography and Western blotting, respectively.

RESULTS
The rate of synthesis of 35S-labelled proteoglycans and their rate of loss from the matrix were greater in pathologic tendons. Fluorography and Western blotting showed that the majority of the radiolabel was associated with large proteoglycans (aggrecan and versican) present in the extracellular matrix of pathologic tendon at the beginning of the culture period. These large proteoglycans were rapidly lost from the matrix of this tissue with time in culture compared with small leucine rich proteoglycans. The rate of loss of small leucine rich proteoglycans in pathologic tissue was comparable with the rate of loss observed in normal patellar tendon.

DISCUSSION
The increase in the rate of synthesis of proteoglycans in pathologic patellar tendon compared with normal tissue was due to the elevated synthesis of the large proteoglycans, aggrecan and versican. The overall rate of loss of 35S-labelled proteoglycans from the extracellular matrix of pathologic human patellar tendon was greater than the rate measured in normal tendon. This was primarily due to the loss of the radiolabelled large proteoglycans that were more abundant in the pathologic tissue where the majority of these proteoglycans were lost from the tissue in the first 4 days of the culture period. These results do not differ from normal tissue where large proteoglycans are catabolised rapidly in normal tendons compared to small proteoglycans that are lost at a much slower rate (2). Together these observations suggest that the main difference between the normal and pathologic tendons is in the rate of synthesis of large proteoglycans whereas the rates of loss of the two different proteoglycan species follows the pattern observed in the normal tissue. Increased cellularity has been reported in a number of studies to be associated with overuse tendinopathy. It is therefore likely that as the result of the underlying pathology, more cells are present in the tissue thereby producing a net increase in tissue proteoglycans.

Overall these data support the concept that tendons exhibiting overuse tendinopathy are characterized by an altered extracellular matrix that has a different composition, structure and metabolism compared to normal tendon and that these changes result in part from the increased synthesis of large proteoglycans that are rapidly lost from the extracellular matrix of pathologic tendon. This indicates that the extracellular matrix of tendon exhibiting overuse tendinopathy is a dynamic structure characteristic of an attempted adaptive or healing process.

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INTRODUCTION
The incidence of tendinopathy is high among both athletes and the general population, and the knowledge about both the etiology and structural together with physiological changes is still very sparse. The aim of the present study was to elucidate to what extent tendinopathy initiates focal physiological and structural changes in the tendon tissue.

METHODS
An analysis of different gene expressions (N=18) and Transmission Electron Microscopy (n=14) in two tendon biopsies from the same tendon, one biopsy from the maximal tendinopathic and one biopsy from a normal area of the tendon, in Achilles Tendinopathy patients were taken.

RESULTS
We observed that Collagen 1, Collagen 3, Fibronectin, Tenascin C, TGF-b and Fibromodulin was significantly increased in the tendinopathic area of the Achilles tendon compared with healthy tissue and Decorin showed a tendency of decrease in the tendinopathic tissue, indicating a higher collagen synthesis in tendinopathy. Additionally MMP-2, MMP-9 and TIMP 2 were significantly increased in the tendinopathic tissue while no changes could be observed in TIMP-1, indicating a higher collagen breakdown in tendinopathy. Scleraxis, lysyl oxidase and tenomodulin were not significantly different between the two conditions, leading to the suggestion that fibrillogenesis is not present in tendinopathy. Furthermore bFGF, cmet and ki67 was significantly decreased and CTGF, HGF, VEGF, IGF, showed no significant differences between the two conditions, indicating no ongoing wound healing process in these patients. Likewise the inflammatory factors COX-1, IL-1R, IL-1b, CCL and IL-6 showed no significant changes between healthy and tendinopathic tendon tissue. The gene expression of Substance P was likewise not significantly different between the two conditions of the tendon. The density and Mean area of collagen fibrils were significant different between the biopsies from the tendinopathic area of the tendon compared with the normal area of the tendon. The tendinopathic part of the tendon showed significant more fibrils per uM² with a small diameter and mean area compared to the healthy tendon.

CONCLUSION
In summary, several gene expressions changed with tendinopathy indicating an increased collagen turnover in tendinopathy. Further theses changes in gene expression might have promoted the structural changes of the collagen fibrils taking place in tendinopathy. Since no signs of fibrillogenesis, inflammation or wound healing could be detected, these study supports that tendinopathy is an ongoing degenerative process.
EVIDENCE OF ACCUMULATED STRESS IN ACHILLES AND ANTERIOR KNEE TENDONS IN ELITE BADMINTON PLAYERS.

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INTRODUCTION

Tendon related injuries are a major problem but the aetiology of tendinopathies is unknown. In tendinopathies as well as during unaccustomed loading intra-tendinous flow can be detected indicating that extensive loading can provoke intra-tendinous flow.

The aim of present study is to evaluate the vascular response as indicated by colour Doppler (CD) activity in both the Achilles and patella tendon after loading during high-level badminton matches.

METHODS

The Achilles tendon was subdivided into a mid-tendon, pre-insertional, and insertional region and the anterior knee tendons into a quadriceps-, patella- and tuberositas region. Intra-tendinous flow was measured using both a semi-quantitative grading system (CD grading) and a quantitative scoring system on colour Doppler (CF inside region of interest). Intra-tendinous flow in the Achilles and anterior knee tendons was examined in fourteen single players before tournament and after 1st and 2nd match respectively on both the dominant and non-dominant side.

RESULTS

All players had abnormal intra-tendinous flow (Colour Doppler ≥ grade 2) in at least one tendon in at least one scan during the tournament.

At baseline, only two of the 14 players had normal flow in all the tendons examined. After 1st match, tendencies to higher intra-tendinous flow were observed in both the dominant patella tendon and non-dominant quadriceps tendon (p-values n.s.). After 2nd match intra-tendinous flow was significant increased in the dominant patella tendon (P= 0.009). In all other locations there were a trend towards a stepwise increase in intra-tendinous flow.

DISCUSSION

This is the first study that has followed elite players after two consecutive matches. The preliminary results indicate that high amount of intra-tendinous flow was found in elite badminton players at baseline and was increased after repetitive loading, especially in the patella tendon (dominant leg). The colour Doppler measurement can be used to determine changes in intra-tendinous flow after repetitive loading.
MECHANICAL STIMULATION OF TENDON HEALING: WHEN AND HOW?

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INTRODUCTION

The healing of tendon injuries is dependent on mechanical loading, and early loading is subject for clinical studies (1). However, little is still known about the optimal loading conditions for tendon healing in vivo. We have performed a number of studies on the effects of short controlled loading episodes on otherwise unloaded healing Achilles tendons, in rats.

Research questions: Are short daily loading episodes sufficient to stimulate healing? Is one single loading episode sufficient, and low long do the effects last? Which loading parameters are important; duration, magnitude or frequency? Have mechanical loading different effects during different phases of healing?

METHODS

We transected the right Achilles tendon and removed a 3 mm segment. The tendons were thereafter left to heal unsutured meanwhile unloaded by tail-suspension. This method ensured a complete unloading, but still allowed short well-defined loading episodes, during which the rats were running on a treadmill. In one study, a vibration-plate was used instead. The treadmill speed was set at 9 or 10 m/min, with an inclination between 0 and 25 °. The duration of the loading episode was 15-60 min each day. The experiments so far were evaluated mainly by mechanical testing, although histology and molecular biology methods were also applied.

RESULTS

Daily loading episodes for 12 days increased tendon callus strength. The peak force was doubled by running for 15 min compared to unloaded controls (p=0.001). However, full time free cage activity was in turn almost 50% stronger than the groups with short loading episodes (p≤0.002). The same pattern was found for stiffness. There was basically no difference in peak stress and elastic modulus in any of the groups. There was only a weak correlation between loading time and peak force (r²=0.21; P=0.015). The results also showed that an additional daily 15 minutes loading episode, 8 hours after the first, did not further improve healing.

Loading during day 2-5 after transection increased the peak force after 8 days by 60% compared to unloaded controls (p=0.01). Loading during day 8-11 produced a 50% higher peak force at day 14 (p=0.006). In both cases, there was also a 40% increase in peak stress (p=0.05 and p=0.03). Even as little as 30 min of loading once, was sufficient to increase peak force 7 days later by 20%. This response was not apparent after only 3 days.

Vibration exercise did not improve the peak force of the tendon or any of the other parameters. Uphill-running showed no additional effect compared to normal running.

DISCUSSION

Loading had a dramatic effect on peak force and cross-sectional area, but mostly not on the tissue quality. However, improved tissue quality was sometimes observed when tendons were unloaded for 3 days before evaluation. This suggests that the immediate response to loading mainly involves proliferation, followed by a later differentiation.

The absent effect of a second loading episode after 8 hours suggests that the tissue "remembered" the stimulation from the first loading. Even though treadmill running increased the strength dramatically, free cage activity still was more effective. There was only weak time effect of duration of loading, implying that something else defines the optimal type of loading stimulus.

Loading increased the strength of the healing tendon tissue both during the early phase and the later, phase. The effect on early healing was a bit unexpected, since the mechanical stimulation was applied on a fragile callus during the inflammatory phase. Nevertheless, this result is consistent with our previous finding that the expression of some inflammation-related genes is reduced by mechanical loading in the early healing (2). The histological evaluation, however, indicated that bleeding was somewhat increased in the loaded animals.

The vibration exercise did not improve the healing outcome at any of the parameters. This could imply that the frequency of the loading changes is not very important, however we have only studied one frequency and we don’t know how much of the vibration from the plate was transformed into mechanical forces in the tendon.

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THE COL5A1 GENE AND MUSCULOSKELETAL SOFT TISSUE INJURIES

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INTRODUCTION

The BstUI restriction fragment length polymorphism (RFLP) within the COL5A1 gene has been shown to be over-represented in asymptomatic participants when compared to those with chronic Achilles tendinopathy (TEN) (1-2) and asymptomatic female participants when compared to those with anterior cruciate ligament (ACL) ruptures (3). The frequency of the CC genotype of the asymptomatic male participants (±28 years) in the ACL study (16%) was distinctly different to the frequency of the older controls in the TEN studies (±39 years), as well as the female (±28 years) ACL study asymptomatic groups (24-27%). Since participants in the ACL study were approximately 10 years younger than those in the tendinopathy studies, the aim of this study was to determine whether the distribution of the COL5A1 BstUI RFLP within the combined asymptomatic participants without any known history of tendon injuries is age-dependent, particularly among males.

METHODS

All the 496 asymptomatic participants (265 male and 231 female) without any reported history of any tendon injuries that were previously investigated in three separate publications were included in this analysis (1-3). The participants were combined and divided into three male and three female age groups; (1) ≤25 years old, (2) 26 to 42 years old, and (3) ≥43 years old. A one-way analysis of variance (ANOVA) was used to determine any significant difference between the characteristics of the male and female age-groups. A chi-squared ($\chi^2$) test, Fisher’s exact test or $\chi^2$ test for linear trends was used to analyse any differences in the genotype and any other categorical data between the groups.

RESULTS

When the 265 male asymptomatic participants from all studies were pooled and divided into age-group tertiles, there was a significant linear increase in the COL5A1 CC genotype frequency (P=0.032) amongst the male age groups, with the youngest group having the lowest (13%) and the oldest group the highest (27%). There was however a similar CC genotype content in all three female (n=231) age groups (24 to 27%, P=0.795).

DISCUSSION

There was an age-dependant significant increase in distribution of the COL5A1 BstUI RFLP CC genotype within the pooled asymptomatic male participants of the three studies which previously investigated this polymorphism as a possible risk factor for soft tissue injuries. We propose that the reported finding indicates that the youngest group of asymptomatic male participants consists of a mixture of individuals, similar to the general population, who are at low and high risk of musculoskeletal soft tissue injuries. However, when older subjects (which would have had a greater amount of exposure to extrinsic factors) are analysed, individuals which may have been previously uninjured, would have developed an injury. Therefore, when older asymptomatic participants are analysed, the group will contain a highly selected sample of the population which are at low risk of Achilles tendinopathy and/or ACL ruptures. The practical implication of this finding is that the selection of control groups is of critical importance when future studies of this nature are designed. Future research investigating this genetic variant as a risk factor for soft tissue injuries should consider the findings of this study when selecting an asymptomatic control group.

REFERENCES

RANGE OF MOTION MEASUREMENTS DIVERGE WITH INCREASING AGE FOR \textit{COL5A1} 3'-UNTRANSLATED REGION GENOTypes

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INTRODUCTION

Both an increased and decreased joint range of motion (ROM) are potential modifiable risk factors for chronic Achilles tendinopathy. Several genetic components have recently been shown to be associated with these injuries. Specifically, variants of the \textit{BstUI} Restriction Fragment Length Polymorphism (RFLP), within the 3'-untranslated region (UTR) of the \textit{COL5A1} gene, were found to be significantly associated with chronic Achilles tendinopathy in a South African (1) and an Australian (2) cohort. In addition, Heritable Disorders of Connective Tissue, which have a unifying symptom of joint hypermobility, are caused by mutations within the \textit{COL5A1} gene (3). Furthermore, the \textit{COL5A1} BstUI RFLP is associated with ROM measurements in a mixed injured/uninjured cohort (4). \textit{COL5A1} encodes the pro-\alpha1 chain of type V collagen, a minor fibrillar collagen that modulates fibrillogenesis. The aim of this study was therefore to investigate the association between the \textit{COL5A1} BstUI RFLP and sit and reach (SR) ROM in an apparently healthy and physically active cohort.

METHODS

The SR test was performed on 325 White subjects (204 male, 121 female). Subjects were genotyped for the BstUI RFLP (C/T) within the \textit{COL5A1} gene.

RESULTS

The \textit{COL5A1} BstUI RFLP genotype was only associated with SR ROM in older (\textit{\geq}35 years) subjects (TT: 225 \pm 96 mm, TC: 245, \pm 100 mm, CC: 321 \pm 108 mm, N=96, p=0.017). A significant interaction between age and \textit{COL5A1} BstUI RFLP genotype explained the difference in SR ROM between the genotype groups. Together, sex and \textit{COL5A1} genotype, accounted for 22.8\% of the variance in SR ROM in the older group.

DISCUSSION

The \textit{COL5A1} BstUI RFLP is associated with SR ROM, particularly with increasing age. The CC genotype may be “protected” against the age-related decline in ROM. This genotype has also been shown to “protect” individuals from developing chronic Achilles tendinopathy (1-2). The \textit{COL5A1} BstUI genotype should be considered as an important contributing factor to ROM variation, particularly in older, apparently healthy and physically active individuals. The possible relationship between chronic Achilles tendinopathy, ROM and sequence variation within the \textit{COL5A1} gene warrants further investigation.

REFERENCES

IS GLUTAMATE SIGNALING OF IMPORTANCE FOR THE MUSCULOSKELETAL SYSTEM?
– STUDIES ON MYOSITIS IN RESPONSE TO MUSCLE OVERUSE AND INJECTIONS INTO THE LOOSE PARATENDINOUS TISSUE OF THE ACHILLES TENDON

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INTRODUCTION
Glutamate is an excitatory neurotransmitter of importance in situations with pain. There is very little information on glutamate for the musculoskeletal system. It has nevertheless been observed that there are higher levels of free glutamate in chronically painful Achilles tendons (tendinopathy) than in normal Achilles tendons [1]. Evidence of glutamate release by tendon cells has also been noted and this evidence was found to be more pronounced for tendinopathy with tendinosis (degenerative-like tissue changes) than for normal tendons [2].

It is not known as to whether there is a glutamate signaling system in other parts of the muscles including the muscular tissue as such. That includes the situation when there is muscle inflammation (myositis).

In the present study we therefore wanted to evaluate for the possibility that there is a glutamate signaling system not only in tendons but also in muscle tissue.

METHODS
An experimental model using rabbits leading to both myositis and tendinosis-like changes of the triceps surae muscle and the Achilles tendon, respectively, was used. It conforms to a certain extent to an overuse model (“kicking machine”) affecting the triceps surae muscle previously used [3]. However, injections were also given in the loose connective tissue surrounding the Achilles tendon (paratendinous connective tissue). The injections corresponded to substance P (SP) and the endopeptidase inhibitors Captopril and DL-Thiorphan. The muscle overuse was maintained for 2 hours every second day (4 sessions in total). Immunohistochemistry and antibodies against the glutamate transporter VGluT2, the glutamate receptor NMDAR1, and markers for inflammatory cells were applied. In situ hybridization for demonstration of mRNA for VGluT2 was also applied. The soleus part of the triceps surae muscle was evaluated.

RESULTS
A myositis developed in the overused muscles. Infiltrates of inflammatory cells were thus to varying extents observed. Interestingly, the inflammatory cells exhibited immunoreactions for VGluT2 as well as NMDAR1. Double-staining showed that the same cells showed reactions for both substances. Double-staining furthermore showed that some of the immunoreactive cells were reactive for T cell/neutrophil marker and others for eosinophil marker. Via in situ hybridization, it was found that inflammatory cells exhibited mRNA for VGluT2.

DISCUSSION
The existence of a glutamate signaling system for muscle tissue has here for the first time been shown. It was found to be related to the inflammatory cells in myositis. The observations suggest that glutamate-mediated autocrine/paracrine effects occur during development of musculoskeletal inflammation. These findings and previously made observations concerning tendons make clear that further studies on the importance of glutamate signaling in muscle and tendon disorders should be performed. Should treatment that interferes with glutamate effects be considered in such disorders?

REFERENCES
USING FTIR TO DIFFERENTIATE ROTATOR CUFF TEARS AND IDENTIFY TREATMENT BIOMARKERS

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INTRODUCTION

Surgical repair of rotator cuff tendons (RCT) have a high failure rate, particularly for larger tears. Better characterization of the underlying biochemical changes in RCT tears may guide more accurate and reliable identification of pathology, and guide effective management. This study aimed to identify biomarkers of rotator cuff tear pathologies to aid accurate identification and monitoring of disease progression. FTIR provides unique biochemical fingerprints of tissue specimens. All molecules are excited to higher vibrational states at specific wavelengths, which can be used to identify the chemical composition of tissues.

METHODS

The chemical composition of 95 formalin-fixed RCTs were measured from patients aged 20-89. 81 RCTs were classified according to the size of tear as partial, small, medium large and massive. These torn RCTs were compared to 14 uninjured RCTs. Two 3 mm circumferential punch biopsies were taken from each patient and preserved in formalin. A FTIR spectrometer with an attenuated reflection tip was used to collect spectra for each sample across 400-7000 cm⁻¹ wavelengths. The spectra were reduced and classified using multivariate analysis: principal component analysis, partial least square and discriminant function analysis.

RESULTS

Hierarchical cluster demonstrated that normal and torn tendons could be clearly differentiated, and RCTs could be distinguished by tear size. The first two principal components accounted for 96.55% of variance. The discriminating spectral regions identified include (i) lipids/carbohydrates/phospholipids (1030-1200 cm⁻¹), (ii) collagen structural conformation (1300-1700, 3000-3350 cm⁻¹) and (iii) lipids (2800-3000 cm⁻¹).

DISCUSSION

FTIR can clearly distinguish between normal and different sizes of RCT tears. This study indicates that the onset of RCT tear pathology is mainly due to an alteration of collagen structural arrangements, with associated changes in lipids and carbohydrates. The approach described is rapid and has the potential to be used per-operatively to determine tendon quality and the extent of disease, thus guiding surgical repairs.
MECHANICAL SUITABILITY OF EXTRACELLULAR MATRIX GRAFTS TO AUGMENT REPAIRS OF HUMAN ROTATOR CUFF TEARS

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INTRODUCTION
Rotator cuff tendon (RCT) repairs are associated with high failure rates. Attempts to circumvent and improve post-operative outcomes have resulted in increasing use of grafts to augment repairs. The only mechanical assessment of some RCT repair grafts to-date involved tensile testing alone, and included comparisons to canine infraspinatus. As the shoulder is subject to shear as well as uniaxial loading, we compared the response of repair grafts and human rotator cuff tendons to shearing mechanical stress using dynamic shear analysis (DSA), a novel technique to study material deformation.

METHODS
The shear properties of four RCT repair grafts were measured (Restore, GraftJacket, Zimmer Collagen Repair and SportsMesh). 79 torn RCT specimens were obtained from the edge of RCT tears during surgery from patients aged 22-89 years and compared to 18 matched intact controls. 3mm punch biopsies were taken from the grafts and the tendons, and subjected to oscillatory deformation under compression. The bulk storage modulus (G') was calculated and used as an indicator of mechanical integrity.

RESULTS
We report significant differences in the storage modulus of the different repair grafts (P < 0.05, one-way ANOVA). Zimmer collagen repair had the highest storage modulus, followed by SportMesh, with Restore patches demonstrating the lowest shear values. All tendons however had significantly lower shear values than normal and torn RCTs (P < 0.01, Dunn's multiple comparison test).

DISCUSSION
The large volume of failing RCT repairs demands a better understanding of the mechanical properties of repair grafts. Current RCT repair grafts display a wide variation in their shear mechanical properties. None of the studied repair patches have shear mechanical properties which closely and how closely match human rotator cuff tendons. It is hoped that this study will offer additional information for surgeons when selecting appropriate RCT repair grafts.
INTRODUCTION

Improved understanding of the biomechanics of rotator cuff tendons may help reduce high re-rupture rates observed after rotator cuff repairs. This study aims to develop a novel method for quantitatively determining differences in the mechanical properties of intact healthy rotator cuff tendons in comparison to torn ‘diseased’ tendons. A common problem in the mechanical testing of small tendon samples is that stress risers at the clamp-tendon interface can obscure measurements. We present a novel solution using Dynamic Shear Analysis (DSA).

METHODS

Rotator cuff tendon specimens were obtained during shoulder surgery from 97 patients. There were 79 tears, which were classified according to the size of the tear and compared to 18 controls matched for age and sex. All 3mm-sized biopsy samples were subjected to DSA using oscillatory deformation under compression. The storage modulus (G’) was calculated and used as an indicator of mechanical integrity.

RESULTS

Healthy intact tendons had a significantly higher modulus than torn tendons, indicating that torn tendons are mechanically weaker than normal tendons (p = 0.032, unpaired t-test). The modulus of different tear sizes showed that normal tendons had significantly higher storage modulus than tendons with small and massive tears (p<0.01, Bonferroni’s multiple comparison test). Importantly, the measured moduli did not otherwise significantly correlate with age, sex, hand dominance, or length of preservation in formalin (p > 0.05).

DISCUSSION

DSA allowed us to demonstrate in this case control study that normal rotator cuff tendons have a significantly higher modulus than torn tendons, indicating that torn tendons have less mechanical integrity (p=0.032). Our study further demonstrated a trend between increasing tear size and decreasing mechanical integrity. High failure rates of repairs suggest that there is an inherent physiological and biochemical defect in torn tendons, which may be less able to withstand mechanical loads following repair.
CHARACTERIZING DIFFERENCES IN THE COLLAGEN STRUCTURAL COMPOSITION BETWEEN NORMAL AND TORN ROTATOR CUFF TENDONS USING DIFFERENTIAL SCANNING CALORIMETRY

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INTRODUCTION

Repairs of massive rotator cuff tendon (RCT) tears have higher failure rates than small RCT tears, although the pathophysiology is not fully understood. As RCTs are primarily composed of collagen, its structural changes could alter tendon mechanical properties, as previously demonstrated in dermis. This study aimed to quantify if differences in collagen structure and integrity existed between normal, small and massive RCT tears. Using differential scanning calorimetry, collagen undergoes detectable conformational and chemical changes during heating.

METHODS

27 human biopsies were taken intra-operatively from 9 small, 9 massive tears and 9 normal RCTs in this pre-powered study. 3 snap frozen samples were taken from each patient. Samples were heated between 20-80°C. The melting temperature (TM), denaturing temperature (TD) and denaturation enthalpy (ΔH) were measured. TM is proposed to represent amide bond breakage, causing increased protein chain mobility. TD reportedly corresponds with proteins falling out of solution. ΔH should correlate with the relative amount of triple helical structure. Polarised light microscopy allowed quantitative validation.

RESULTS

Massive RCT tears had significantly higher TM and TD compared to small RCT tears and normal RCTs (P<0.05). ΔH was not significantly changed. Histology of massive tears demonstrated greater collagen structural disruption compared to other groups (P<0.05).

DISCUSSION

These novel findings suggest greater quantifiable collagen structural disruption in massive tears, compared to normal and small tears. This study using differential scanning calorimetry offers insight into possible mechanisms for, or adaptation to, higher RCT failure in larger tears and reduced strength.
CHARACTERIZATION OF HUMAN ACHILLES TENDON CELLS IN RESPECT TO EFFECTS OF SUBSTANCE P STIMULATION IN VITRO

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INTRODUCTION
Despite recent advances, the aetiology and pathogenesis of tendinopathy have not been clearly elucidated. It is, however, apparent that the tendon tissue in tendinopathy patients exhibits marked degenerative-like changes (‘tendinosis’). At the cellular level, tendon cells in tendinosis tissue have been shown to produce an array of signal substances that was once thought to be restricted to neurons. This includes the neuropeptide substance P (SP), but also catecholamines, glutamate, and acetylcholine. In turn, because the tendon cells also possess receptors for these signal substances, including the preferred receptor for SP (the neurokinin-1 receptor [NK-1 R]), it is possible for the cells to act on themselves in an autocrine/paracrine fashion.

Compelling evidence suggests that SP results in prominent effects when administrated to connective tissue, such as cell proliferation, collagen deposition, and apoptosis. Furthermore, studies have shown that SP can stimulate stem cells differentiation into other cell types. These stem cells, which are more metabolically active and possess different morphology compared to ordinary tendon cells (tenocytes), may play a fundamental role in tendinosis. Therefore, the properties of tendon cells should be examined. The direct effects of SP to induce alterations in human tendon cells have not been investigated in cell culture until now.

In this study, we have established a human tendon cell culture model to compare normal and tendinosis tendon cells, in particular regarding response to stimulation by SP. Concurrently, attempts were made to delineate the characteristics of tendon stem cells from the general tendon cell population.

METHODS
Achilles tendon biopsies from patients suffering from tendinosis, as well as from healthy controls, were grown as primary cultures. Cells from passage 3 to 6 were used to compare the differences in proliferation, receptor levels, endogenous SP production, and stem cell percentage in the cultured population, using various laboratory techniques.

RESULTS
Immunocytochemistry (IHC) and flow cytometry (FACs) demonstrated the presence of NK-1 R on the cultured cells from both normal and tendinosis tissue. ELISA results showed higher levels of endogenous SP production in normal cells as compared to tendinosis ones. With respect to proliferation, normal tendon cells responded in a positive dose-dependent manner, while tendinosis cells exhibited negative or no effects, as the concentration of administrated SP was increased. Through IHC and FACs, a subset of the tendon cell population (1-20%) was positive for the stem cell marker, stage-specific embryonic antigen 4 (SSEA-4).

DISCUSSION
The presence of NK-1 R, the receptor for SP, in both normal and tendinosis samples justified the approach of adding varying concentrations of SP to determine the possible dose-dependent relationship in proliferation of tenocytes. The measurement of SP in cultured cells allowed for the baseline, endogenous SP levels to be taken into account. In addition, it was found that SP levels decreased with increasing passage number, indicating the need to study these cells at earlier passages before phenotypic drifts occur. The proliferation results indicate a positive dose-dependent relationship between SP and rate of proliferation in normal cultured cells. However, the same relationship cannot be seen if the same normal cells were subjected to SP following revival from liquid nitrogen storage. Hence, it is suggestive that the cells responsible for the proliferative effect did not survive the freeze-thaw procedure.

Recent studies have suggested that the erroneous differentiation of tendon stem cells contribute to tendinopathy. The identification of a small subset, within the general cultured tenocyte population, to be positive for the stem cell marker, SSEA-4, holds promise for further analysis of these stem cells. Particularly, additional stem cell makers shall be used for characterization, and parallel studies will review whether these supposed stem cells are positive for SP and NK-1 R. With more knowledge about properties of these cells, it might be possible to isolate them in culture to determine whether they deviate in response to signal substances as compared to ordinary tenocytes.
ENDOGENOUS SUBSTANCE P PRODUCTION INCREASES WITH EXERCISE IN AN ANIMAL MODEL OF TENDINOPATHY – PEPTIDERGIC ELEVATION PRECEDES TENDINOSIS-LIKE TISSUE CHANGES SUCH AS CELL PROLIFERATION AND ANGIOGENESIS

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INTRODUCTION

It has been revealed that tendinopathy is characterized by degenerative-like tissue changes (‘tendinosis’), such as cellular proliferation and angiogenesis, although it is unclear why this occurs. To study the events leading to tendinosis, we have established an animal model for investigation of different stages in the pathophysiology.

Recently, a new hypothesis suggesting the involvement of locally produced neurochemical mediators in the pathology of tendinosis has been proposed. This hypothesis is based on findings of a non-neuronal production of, traditionally neuronal, signal substances by the tendon cells (often collectively called ‘tenocytes’) of human Achilles tendon tissue; findings mainly seen in tissue from patients with tendinopathy. Particularly interesting is the finding of such an endogenous production of the neuropeptide substance P (SP). Studies have also confirmed that tenocytes and blood vessels of the tendon express the preferred receptor for SP, the neurokinin-1 receptor, in both man and rabbit, making these structures susceptible to SP-stimulation. However, the exact role of SP in tendinosis is unclear. It is not known whether there is a significant increase of the local SP-production in tendinosis tissue, nor if such an increase precedes the tissue changes or if it is just a mere byproduct of the latter. Therefore, in this study, the endogenous production of SP at different stages of exercise in our animal model was measured. Furthermore, the study aimed at investigating the source of the locally produced SP.

METHODS

Four groups of six New Zealand white rabbits were used. Animals were subjected to our established protocol of electrical stimulation and passive flexion-extension of the right triceps surae muscle every second day for 1, 3 or 6 weeks. One group was subjected to no training at all (untrained controls). ELISA was performed on specimens from both the experimental (exercised), side and the contralateral (unexercised) side to measure the levels of SP. Immunohistochemistry (IHC) and in-situ hybridisation (ISH) were performed to investigate the location of SP in the tissue. Kruskal-Wallis test (K-W), followed by pair-wise Mann-Whitney U test (M-W U), with Bonferoni correction, was performed on the data obtained from the ELISA.

RESULTS

ELISA revealed significantly increased levels of endogenously produced SP in the Achilles tendon from the exercised limb in all the experimental groups as compared to the control group (see figure on the right; K-W: p=0.01; M-W U: *: p<0.05, **: p<0.01). In the unexercised limb, the levels were also increased in all experimental groups, although this was not significant (K-W: p=0.14). IHC illustrated reactions of SP mainly in blood vessel walls, both in arteries and venoles. ISH confirmed presence of SP mRNA in these cells.

DISCUSSION

This study shows that the intratendinous production of SP is elevated already after 1 week of exercise in this particular animal model for tendon overload. That is interesting, considering the fact that we have previously shown that the tendinosis-like tissue changes in the rabbit Achilles tendon (hyperlcellularity and vascular proliferation, same as for human tendinosis) occur only after a minimum of 3 weeks of exercise. This would indicate that increased endogenous SP-production precedes tendinosis; making theories on the involvement of SP in the early stages of tendinosis pathophysiology more plausible, especially if one bear in mind that SP is known to have proliferative effects on fibroblast and also to promote angiogenesis. The study furthermore indicates that the main source of the local SP-production might be cells of the blood vessel walls, although other sources cannot be excluded.

We have previously demonstrated that tendinosis-like tissue changes also occur in the contralateral (unexercised) Achilles tendon to the same degree as on the exercised side in this model. The present study shows, although not significant, that SP-production is also increased on the contralateral side in the experimental groups, suggesting the involvement of central neuronal mechanisms.

In conclusion, this study confirms observations from research on man that there is a production of SP in the Achilles tendon, and furthermore verifies that this production is significantly increased when the tissue undergoes development of tendinosis; the SP elevation preceding the tendinosis-like tissue changes.
A POTENTIAL LINK BETWEEN ACHILLES TENDINOPATHY RISK AND ENDURANCE RUNNING ABILITY

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INTRODUCTION

Previous research has identified the COL5A1 gene BstUI restriction fragment length polymorphism (RFLP) as a risk factor for Achilles tendinopathy in two independent populations (1,2). The COL5A1 gene codes for the alpha-1 chain of type V collagen. Type V collagen is believed to initiate fibril assembly and regulate lateral fibril growth. The COL5A1 gene BstUI RFLP has also been shown to be associated with measures of flexibility (3). Since flexibility has been correlated with endurance running performance, the purpose of this study was to investigate if the COL5A1 gene BstUI RFLP associates with endurance performance during the 226km South African Ironman triathlon.

METHODS

Three hundred and thirteen Caucasian male participants who completed either the 2006 or the 2007 226km South African Ironman triathlon (3.8km swim, 180km bike, 42.2km run) participated in this study. All participants were genotyped for the COL5A1 BstUI Restriction Fragment Length Polymorphism (RFLP).

RESULTS

The COL5A1BstUI RFLP was significantly associated with time to complete the running component of the triathlon. Participants with a TT genotype completed the running component of the race significantly ($P=0.019$) faster than individuals with a CC genotype. There were no significant genotype differences for time to complete the swim, the bike, or the overall race. The COL5A1 BstUI RFLP, BMI, age and running training during the last 15 weeks predicted 30% of the variance in the time to complete the run.

CONCLUSION

This is the first study to identify the COL5A1 BstUI RFLP as a marker for endurance running performance. Although stiffness was not measured in this study, we speculate that individuals with a TT genotype of the COL5A1 BstUI RFLP have an increased musculoskeletal stiffness and therefore greater running economy. As previous research has shown that individuals with a CC genotype were protected against developing Achilles tendinopathy, we further speculate that individuals at increased risk of tendinopathy also have a more favourable endurance running phenotype. Further research is required to further elucidate the link between genetics, flexibility, athletic performance and injury risk.

REFERENCES

THE POLYGENIC PROFILES IN PARTICIPANTS WITH ACHILLES TENDINOPATHY AND CONTROLS

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INTRODUCTION
Achilles tendinopathy is a multifactorial condition for which various genetic risk factors have been identified. More specifically, five single nucleotide polymorphisms (SNPs) have been associated with and/or suggested to be implicated in Achilles tendinopathy. These SNPs are (1) the \textit{COL5A1} gene BstUI restriction fragment length polymorphism (RFLP), (2) the \textit{MMP3} rs679620 polymorphism, (3) the \textit{GDF5} rs143383 polymorphism, (4) the \textit{IL1B} -511 polymorphism, and (5) the \textit{IL6} -172 polymorphism. This study uses a polygenic profile, as originally proposed by Williams and Folland (1), to establish if inter-individual risk of Achilles tendinopathy can be explained by combining all five previously identified SNPs.

METHODS
All five polymorphisms have been previously genotyped in 69 South African Caucasian participants with Achilles tendinopathy (TEN) and 93 South African Caucasian control participants with no previous history of Achilles tendinopathy (CON). Using the model developed by Williams and Folland (1), the “total genotype score” (TGS) was calculated from the accumulated combination of each of the five single nucleotide polymorphisms. Individual genotypes were each given a “score” of 2, 1 or 0. The homozygote genotype most closely associated with an increased risk of Achilles tendinopathy was given the score “2”; heterozygote’s were scored 1 and the homozygote most closely associated with reduced risk of Achilles tendinopathy were scored 0. Participants were “scored” as follows: \textit{COL5A1} BstUI RFLP TT=2, TC=1, CC=0; \textit{MMP3} rs679620 GG=2, AG=1, AA=0; \textit{GDF5} rs143383 TT=2, TC=1, CC=0; \textit{IL1B} -511 CC=2, CT=1, TT=0; \textit{IL6} -172 CG=2, GC=1, CC=0. TGSs were calculated by multiplying the sum of the five individual genotype scores (GS) by 100 and dividing by 10. Receiver operating characteristic (ROC) curves were used to evaluate the ability of the TGS to correctly distinguish participants at high and low risk of Achilles tendinopathy. The area under the ROC curve (AUC) and 95% confidence interval was calculated. Significance was accepted when \(P<0.05\).

RESULTS
The TGS of the TEN participants (TGS=63.6±15.3, kurtosis statistic: -1.023±0.570) was significantly greater \((P<0.001)\) than the CON participants (TGS=54.3±16.3, kurtosis statistic: -0.331±0.495). ROC analysis showed a significant discriminating accuracy of TGS to identify risk of Achilles tendinopathy in a South African population (AUC=0.64; 95% CI: 0.56-0.73; \(P=0.002\)).

CONCLUSION
The current study demonstrates that polygenic profiles, as proposed by Williams and Folland (1), are able to discriminate between participants with Achilles tendinopathy and controls. This is a novel method that allows various genetic risk factors to be evaluated collectively. Such methods should be used to when developing multifactorial models to identify athletes at increased risk of Achilles tendinopathy.

REFERENCES
A PATHWAY-BASED APPROACH INVESTIGATING IL-1Β, IL-6 AND IL-1RN PROVIDES NEW INSIGHT INTO THE GENETIC SUSCEPTIBILITY OF ACHILLES TENDINOPATHY.

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INTRODUCTION
Achilles tendinopathy (AT) is a multifactorial condition for which genetic risk factors have been identified (1-3, 5). Expression of several inflammatory cytokines and signalling molecules are altered in tendinopathy (4). A pathway based approach was used to investigate genes within the inflammatory pathway.

METHODS
Functional polymorphisms within \textit{IL-1β} (-31T>C and -511C>T), \textit{IL-1RN} (VNTR) and \textit{IL-6} (-172G>C), were investigated for associations with AT in a South African (SA) and Australian (AUS) case-control study. A total of 356 (158 SA and 198 AUS) asymptomatic control participants (CON) and 171 (89 SA and 82 AUS) participants with AT (TEN) were genotyped. Genotype pairs were constructed using the above polymorphisms in combination with the \textit{COL5A1BstUI} CC genotype.

RESULTS
All risk-reducing genotypes in combination with the \textit{COL5A1BstUI} CC genotype significantly modulated risk of AT ($p<0.025$). No associations were observed for \textit{IL-1β} -31T>C, \textit{IL-1β} -511C>T or \textit{IL-1RN}. The GG genotype (OR = 2.1, 95% CI 1.2– 3.6; $p=0.017$) and G allele (OR = 1.5, 95% CI 1.0– 2.2; $p=0.044$) of \textit{IL-6} -172G>C were significantly over represented in AUS TEN.

DISCUSSION
Variations within interleukins genes together with the \textit{COL5A1BstUI} CC genotype are able to modulate risk of AT. This research emphasises that a pathway-based genetic association study may be a more effective approach to capture and understand the genetic risk factors underlying multifactorial conditions, such as AT.

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THERE IS A MORPHOLOGIC CORRELATE FOR AUTOCRINE/PARACRINE TNF-ALPHA EFFECTS IN THE HUMAN ACHILLES TENDON: PARTICULARLY EVIDENT FOR TENDINOSIS TENDONS

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INTRODUCTION
Mid-portion Achilles tendinosis is a frequent condition affecting both physically active and sedentary persons. The background to this condition is not totally clear. TNF-alpha is a cytokine with pro-inflammatory and modulating functions. It has been discussed as to whether this cytokine is involved in the function of the normal and chronic painful (tendinosis) Achilles tendons. Anti-TNF treatment is nowadays frequently used for several conditions of inflammatory character. In preliminary studies on patients with HLA-B27-positive spondyloarthropathy, it is shown that rapid resolution of long-standing insertional Achilles tendon pain may occur after treatment with TNF-alpha antagonists [1]. There is, however, very little information concerning the importance of the TNF-system in the more common overuse mid-portion Achilles tendinosis. As the expression patterns of TNF-alpha and the TNF receptors, including TNFR1 (TNFR1), are unknown for this condition and for the normal Achilles tendon the present study was undertaken.

METHODS
The degrees of immunohistochemical expressions for TNF-alpha and TNFR1 in normal Achilles tendons (from 6 individuals) and Achilles tendons of patients with mid-portion Achilles tendinosis (from 17 patients) were examined. The patterns of immunoreactions were evaluated and the intensities of immunoreactions were examined using semiquantitative assessment methods.

RESULTS
We noted that specific reactions for TNF-alpha indeed were detected in the tenocytes. However, the intensity of stainings was similar in controls as for tendinosis patients (p=0.368). Morphologically, it was observed that the tenocytes that showed the characteristic tendinosis appearance (having an oval/widened shape) showed the most marked immunoreactions.

Specific reactions for TNFR1 were also detected for the tenocytes. In this case, it was found that the immunoreaction intensities were significantly greater in mid-portion tendinosis than for controls (p=0.018). Furthermore, it was noted that the tenocytes with a slender and spindle-shaped form exhibited clumps of immunoreactive material along the length of the tenocytes, whereas oval shaped/rounded tenocytes had a more diffuse pattern of immunoreactivity.

DISCUSSION
This is the first report to document that the tenocytes of the human Achilles tendon exhibit immunoreactions for TNF-alpha as well as TNFR1. Previously, immunoreactions for TNF-alpha and TNFR1 have been documented in horse tendons (the superficial digital flexor tendons) (2).

Our results show that there is a morphological correlate for TNF-alpha effects on the tenocytes in the human Achilles tendon and suggest that autocrine/paracrine effects may occur. This appears particularly to be the fact for tendinosis tendons. Indeed, the up-regulation of TNFR1 in tenocytes from patients with chronic Achilles mid-portion tendinosis suggests that the tendons in this condition might have increased sensitivity to the effects of TNF-alpha. However, further studies are needed before considering anti-TNF treatment in tendinosis not associated with HLA-B27. Ongoing studies in our laboratory may hopefully shed further light on this topic.

REFERENCES
INTRODUCTION
The tendinopathy is a frequent injury during the sports practice. Multiple treatments exist. We have created a protocol combining the thermotherapy, the work eccentrics and the administration of arginine as food supplement with sanitary record. We have based on the works of Currwin and Stanish besides the current knowledge.

METHODS
We have realized the protocol in patients who were presenting tendinopathy of different locations, excluding those that had partial tears, calcifying tendon, previous surgery or systemic disease. The protocol has been realized every day, the patients have been taught by a demonstrative video and by a text of treatment; the dose of arginine is of 1500mg a day.

The clinical evaluation has understood the level of activity and visual analogical system (VAS).

RESULTS
36 patients have been treated up to the moment by middle ages of 39 years old, 28 men and 8 women, with a media VAS of 6,07 and one minimal follow-up of 6 months. The patients have presented good to excellent proved in 90 % of the cases.

DISCUSSION
The reasons of failure have been due to abandon of the accomplishment of the protocol, realizing anomalous of the eccentric work that concords with the literature.

The protocol is a good method for the basic treatment of the tendinopathy without other alterations.
INTRODUCTION
The shoulders of the handball players are submitted to an intense work and mobility extremes (especially the dominant arm or thrower). This physical stress determines a major number of injuries. The magnetic resonance (MRI) is frequently utilized as diagnostic method in symptomatic shoulders. There are numerous publications that have evaluated the pathological findings in MR in voluntary symptomatic patients. Nevertheless, the publications we gather is limited having valued the predominant side with regard to the counter wings or the level of activity. The aim is analyze the findings in MRI realized in dominant and not dominant shoulders without some symptom or history of previous pathology of players of elite handball players. The study design was a cohort study.

METHODS
We realized MR of shoulder of the dominant and not dominant side in 16 players of elite in handball (8 men, 8 women), the mean age was 29 years old in men and mean age 21.5 years old in women, and a global mean age was 27.5 years old. The radiological examination by means of MR where images were realized in T1, T2 and gradient ECHO with courts of 3 mm in the axial planes, sagittal, oblique and coronal, using MRI's machine of General Electric of 1.5 teslas. With protocol of shoulder’s study. The patients have been excluded by pain in the shoulder, pain during the clinical exploration, previous of surgery in the shoulder, the goalkeeper. The images will be interpreted by a radiologist expert in the locomotor systems.

RESULTS
There are statistically significant the presence of injury in the cuff rotator depending on the shoulder (p=0.0098), for the distance acromiohumeral and the interaction between distance acromio-humeral and tuberosité major.

DISCUSSION
In our series, there are statistically significant differences in MRI’s findings (dominant and not dominant) for supraespinatus tendon, though we evaluate the difference between the decrease of the internal rotation and the degree injury neither of the labrum glenoideo nor alterations in the posterior capsule. In conclusions, we can find injuries of the cuff rotator in shoulders healthy asymptomatic patients theses aren’t tributary of the surgery.
MARKED OVERUSE AFFECTING THE TRICEPS SURA MUSCLE AND THE ACHILLES TENDON LEADS TO BILATERAL CHANGES IN THE MUSCLE TISSUE OF THE TRICEPS SURA – STUDIES USING A RABBIT MODEL

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INTRODUCTION
A rabbit model (a “kicking machine”) for investigating the effects of marked muscle/tendon overuse concerning the triceps surae muscle has been shown to lead to tendinopathy–like changes in the Achilles tendon. Similar changes occurred on the contralateral side. The purpose of this study was to evaluate what changes that occurred within the muscular tissue when applying the overuse rabbit model. Furthermore, to examine for the possibility that bilateral changes also occurred at the muscular level. A lot of focus was devoted to the neuropeptide substance P (SP).

METHODS
Evaluations after 1, 3 and 6 weeks of exercise (2h of exercise every second day) were made. Passive dorsiflexion and plantar flexion of the right ankle using pneumatic pistons were generated. The right foot, but not the left foot, was attached to the piston. Concentric contractions of the right triceps surae muscle was furthermore achieved using stimulation via surface electrodes. Specimens from the right (experimental) side as well as from the left side were taken. Specimens of the soleus muscle and gastrocnemius muscles were evaluated. Morphologic evaluation, immunohistochemistry (IHC) and ELISA were applied. The IHC and ELISA analyses were devoted to the neuropeptide substance P (SP).

RESULTS
The morphologic appearances of the muscles were affected due to the overuse. That included occurrence of muscle fiber necrosis and an occurrence of an inflammatory response. Changes in morphologic appearances occurred for both sides. SP immunoreactions were noted for inflammatory cells, nerve fibers of thin nerve fascicles and blood vessel walls. Neurokinin-1 receptor (the SP preferred receptor) was expressed in the inflammatory cells and necrotic muscle fibers. The SP levels in the soleus muscles and gastrocnemius were significantly increased in both the exercised and the non-exercised leg after 3 and 6 weeks of training, as compared to non-exercised animals. These measurements were made via ELISA.

DISCUSSION
It is obvious that bilateral changes not only occur for the tendon part (the Achilles tendon) but also for the muscle part when the triceps surae muscle is influenced by marked overuse. It is thus not a good way to have the muscle in the contralateral leg as control tissue. The occurrences of bilateral changes are very interesting and suggest that effects occur via the nervous system. Other factors may also be involved. Further studies on the subject are currently being performed.

REFERENCES
IS TNFALPHA NOT ONLY OF RELEVANCE FOR DISEASED JOINTS BUT ALSO MUSCLES AND TENDONS? – STUDIES ON EXPRESSION OF THE TNF RECEPTOR TYPE I IN MYOSITIS

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INTRODUCTION
Tumour necrosis factor alpha (TNFalpha) is one of the most frequently studied proinflammatory cytokines. Blocking of TNFalpha effects is nowadays used for several inflammatory disorders. It has been suggested that antiTNF treatment may also be of value in tendinosis [1] and blocking of TNFalpha function in a mouse model of Duchenne Muscular Dystrophy is shown to lead to delay and reduction in skeletal muscle breakdown [2]. We have in our laboratory noted that the tendon cells of the human Achilles tendon exhibit immunoreactions for both TNFalpha and the TNF receptor I (TNFRI) (Gaida et al, submitted). Furthermore, that there are expressions of TNFalpha in the inflammatory infiltrates in experimental myositis (Forsgren et al, to be submitted). These observations suggest that TNFalpha effects are to be highly considered both for tendons and the muscular tissue. However, there is a lack of information as to whether TNF receptors are expressed in the inflammatory infiltrates in myositis.

METHODS
A model for myositis in rabbits was utilized. It is a model for overuse of the triceps surae muscle coupled with injections of substance P and endopeptidase inhibitors in the loose paratendinous tissue of the Achilles tendon leading to proinflammatory effects in muscular tissue of the triceps surae muscle and in the outermost parts of the Achilles tendon. This model also leads to tendinosis-like changes within the Achilles tendon [3]. The expression patterns of the TNFRI in the soleus part were analyzed immunohistochemically.

RESULTS
The inflammatory cells in the myositis specimens of the soleus muscle were found to exhibit specific immunoreactions for TNFRI. The reactions were blocked in sections processed with TNFRI antibody that had been preabsorbed with TNFRI antigen. TNFRI immunoreactions were also seen within nerve structures.

DISCUSSION
It is here shown that the inflammatory cells in a myositis model not only express reactions for TNFalpha but also for TNFRI. This suggests that TNFalpha produced by inflammatory cells has effects on these cells in this situation. Thus, autocrine/paracrine effects are likely to occur.

It is possible that TNFalpha effects are more important than previously thought in the modulation of inflammation in skeletal muscle. There is thus a morphologic correlate for TNFalpha effects within the inflammatory infiltrates in myositis. It is likely that the currently used animal model is useful in further studies on the importance of TNFalpha in relation to muscle inflammation.

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THE INFLUENCE OF CYCLICAL LOADING ON EQUINE TENDON IN VITRO – RELEVANT LESSONS FOR THE EFFECTS OF IN VIVO EXERCISE?

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INTRODUCTION

Tendinopathy is significant age-related degenerative disease in humans and horses due to its common occurrence, the lack of a highly effective treatment, the requirement for lengthy rehabilitation, and the risk of reinjury. In horses the superficial digital flexor tendon (SDFT) of the forelimb is the most commonly injured tendon. The SDFT is analogous to the human Achilles tendon because both have a similar elastic modulus, store and releases energy for efficient locomotion, operate at strains that are close to its functional limits, and are predisposed to injury within the tensional (mid) region of the tendon. Repetitive cyclical loading is thought to be a major drive in the degeneration of tendon extracellular matrix (ECM) that precedes these clinical injuries.

In the adult horse, gross mechanical properties do not differ significantly with age or exercise, but show a high variance which may be due to genetic variation and exercise history. Cyclical strain results in an age related decrease in mechanical strength of equine tendon in vitro [1]. In contrast to the young animal, studies in the adult have shown that exercise appears to adversely affect the tendon matrix - regional reductions in collagen fibril diameter were seen in long-term exercised older horses, but not in short-term exercised, younger, horses. The higher proportion of small fibrils in the central region of the long term exercised horses appeared to not correlate with new collagen formation but rather be the result from disassembly of the larger diameter fibrils [2]. Furthermore, in the centre of the tendon where clinical injury is seen, exercise induced loss of glycosaminoglycans (GAG) and another abundant glycoprotein in tendon, Cartilage Oligomeric Matrix Protein (COMP) in older horses [3,4]. From these studies it is hypothesised that, post skeletal maturity, exercise drives degeneration via the loss of constitutive matrix components. We therefore aimed to investigate the mechanisms for this matrix release by applying cyclical loading to tendon explants in vitro.

MATERIALS AND METHODS

Cyclical strain was applied to adult equine SDFT explants (2mm x 2mm x 80mm) mounted in a custom-designed jig in a servohydraulic materials testing device housed within an incubator. Explants were strained at 2%, 5%, 8% or 12% at 1Hz for 20 hours using a sine wave input. Control explants were placed in similar culture conditions but were not cyclically strained. The media was analysed for GAG and collagen release using DMMB and Sirius red binding assays respectively. In addition MMP-2 and -9 levels were measured using zymography, and MMP-13 activity was measured using a fluorogenic substrate. Western blotting and mass spectrometry were used to identify matrix proteins and protein neoepitopes.

RESULTS

Higher strains induced a significant reduction in collagen and cartilage oligomeric matrix protein (COMP) release compared to controls (p≤0.05). In contrast, a strain magnitude dependent increase in GAG release compared to controls was evident (p≤0.05). The increased GAG release was due primarily to aggrecan release. In a significant increase in MMP-derived aggrecan neoepitopes were detected in media from strained explants compared to controls (p≤0.05). MMP-2 and -9 were decreased with strain compared to control tissue and media, while at high strain (12%) MMP-13 activity was significantly increased within the media (p≤0.05).

CONCLUSIONS

Increased strain appeared to displace proteoglycans from the matrix, whilst preserving the collagen network suggesting that these two pools of extracellular matrix proteins are differentially regulated in response to tendon strain. The increase in MMP-13 activity in media with high strain could comprise an initiating step of tendinopathy while exercise regimes that provide strain amplitudes that minimise both processes may be optimal to maintain tendon homeostasis. These findings are consistent with our in vivo studies demonstrating a deleterious effect of exercise on tendon matrix in mature horses and may explain, in part at least, the increasing incidence of tendinopathy with ageing in both horses and humans.

REFERENCES

Influences of paratendinous innervation and non-neuronal substance P in tendinopathy
- studies on human tendon tissue and an experimental model of Achilles tendinopathy

Friday October 1, 2010, at 1.00 pm, Umeå University

Faculty Opponent / External Examiner: Professor David A. Hart, PhD, FCAHS Departments of Surgery, Medicine, and Microbiology & ID McCaig Institute for Bone & Joint Health University of Calgary, Canada

Examination Committee: Dr. Graham Riley, University of East Anglia, United Kingdom Professor Anna Engström-Laurent, Umeå University Professor emeritus Lars-Eric Thornell, Umeå University

Supervisor: Assoc. Prof. Patrik Danielson, Umeå University
Assistant Supervisors: Professor Sture Forsgren, Umeå University Professor Håkan Alfredson, Umeå University
Chairman of Defence Act / Examiner: Professor Mikael Wiberg, Umeå University
Influences of paratendinous innervation and non-neuronal substance P in tendinopathy
– studies on human tendon tissue and an experimental model of Achilles tendinopathy

Gustav Andersson
Thesis from the Dept. of Integrative Medical Biology, Anatomy, and the Dept. of Surgical and Perioperative Sciences, Sports Medicine, Umeå University, 2010

Abstract
Pain of the musculoskeletal system is one of the most common reasons for people seeking medical attention, and is also one of the major factors that prevent patients from working. Chronic tendon pain, tendinopathy, affects millions of workers world-wide, and the Achilles tendon is an important structure often afflicted by this condition. The pathogenesis of tendinopathy is poorly understood, but it is thought to be of multifactoral aetiology. It is known that tendon pain is often accompanied not only by impaired function but also by structural tissue changes, like vascular proliferation, irregular collagen organisation, and hypercellularity, whereby the condition is called tendinosis. In light of the poor knowledge of tendinosis pathophysiology and recent findings of a non-neuronal signalling system in tendon tissue, the contributory role of neuropeptides such as substance P (SP) has gained increased interest. SP, known for afferent pain signalling in the nervous system, also has multiple efferent functions and has been described to be expressed by non-neuronal cells.

As pain is the most prominent symptom of tendinopathy, the focus of the studies in this thesis was the innervation patterns of the tissue ventral to the Achilles tendon (i.e. the tissue targeted in many contemporary treatment methods) as well as the distribution of SP and its preferred receptor, the neurokinin-1 receptor (NK-1R), in the tendon tissue itself. It was hereby hypothesised that the source of SP affecting the Achilles tendon might be the main cells of the tendon tissue (the tenocytes) as well as paratendinous nerves, and that SP might be involved in tendinosis-development.

The studies were conducted, via morphological staining methods including immunohistochemistry and in situ hybridisation, on tendon biopsies from patients suffering from Achilles tendinosis and on those from healthy volunteers. The hypothesis of the thesis was furthermore tested using an experimental animal model (rabbit) of Achilles tendinopathy, which was first validated. The model was based on a previously established overuse protocol of repetitive exercise.

In the human biopsies of the tissue ventral to the Achilles tendon, there was a marked occurrence of sympathetic innervation, but also sensory, SP-containing, nerve fibres. NK-1R was expressed on blood vessels and nerve fascicles of the paratendinous tissue, but also on the tenocytes of the tendon tissue proper itself, and notably more so in patients suffering from tendinosis. Furthermore, the human tenocytes displayed not only NK-1R mRNA but also mRNA for SP. The animal model was shown to produce objectively verified tendinosis-like changes, such as hypercellularity and increased vascularity, in the rabbit Achilles tendons, after a minimum of three weeks of the exercise protocol. The contralateral leg of the animals in the model was found to be an unreliable control, as bilateral changes occurred. The model furthermore demonstrated that exogenously administered SP triggers an inflammatory response in the paratendinous tissue and accelerates the intratendinous tendinosis-like changes such that they now occur after only one week of the protocol. Injections of saline as a control showed similar results as SP concerning hypercellularity, but did not lead to vascular changes or pronounced paratendinous inflammation.

In summary, this thesis concludes that interactions between the peripheral sympathetic and sensory nervous systems may occur in Achilles tendinosis at the level of the ventral paratendinous tissue, a region thought to be of great importance in chronic tendon pain since many successful treatments are directed toward it. Furthermore, the distribution of NK-1Rs in the Achilles tendon described in these studies gives a basis for SP, whether produced by nerves mainly outside the tendon or by tenocytes within the tendon, to affect blood vessels, nerve structures, and/or tendon cells, especially in tendinosis patients. In light of this and of previously known SP-effects, such as stimulation of angiogenesis, pain signalling, and cell proliferation, the proposed involvement of SP in tendinosis development seems likely. Indeed, the animal model of Achilles tendon overuse confirms that SP does induce vascular proliferation and hypercellularity in tendon tissue, thus strengthening theories of SP playing a role in tendinosis pathology.
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