Latest technology in the treatment of chronic recalcitrant tendinopathy

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Tendinopathy

- Tendinopathy is a common condition seen in primary care
- Majority of tendinopathies are self-limiting\(^1,2\) in the early phases\(^3\)
- But over 10% of patients can have persistence of symptoms and fail to respond to routine treatments including physiotherapy
- Tendinopathy with persistence of symptoms >6 months generally results in surgical intervention\(^4,5\)
- Tendinopathy is non life-threatening but is debilitating with significant socio-economic impact\(^2,4-6\)

1 Smidt et al, 2006 *J Rheumatol* 33(10):2053-59
2 Ahmad et al, 2013 *Bone Joint J* 95-B:1158–64
3 Khan et al, 2000 *The Physician and Sportsmedicine* 28(5)
5 Nirschl 2015 *Ann Transl Med* 3(10): 133.
Degenerative tendinopathy, if extensive enough, or if the tendon is placed under high load, can rupture, consistent with 97% of tendons that rupture having degenerative change.

Figure 1  Pathology continuum; this model embraces the transition from normal through to degenerative tendinopathy and highlights the potential for reversibility early in the continuum. Reversibility of pathology is unlikely in the degenerative stage.
Tendinopathy Spectrum

- It is widely accepted that tendinopathies exist in a spectrum of severity

1. Reactive
   - a non-inflammatory proliferative response in the cell and matrix

2. Dysrepair
   - matrix breakdown and disorganisation

3. Degenerative
   - Progression of both matrix and cell changes, cell death / apoptosis

References:
- Wu et al. Arch Orthop Trauma Surg 2011
- Cook & Purdam, Br J Sports Med 2017
Tendon Repair

Without mechanical loading

1. Round cell nuclei
2. Disorientated collagen
3. Low cell proliferation

Without functional tendon cells

1. No **loading-induced** healing response
2. Matrix breakdown
3. Rupture
Table 2  Percentage of autophagic cell death, apoptotic, myofibroblastic and the cell density in the ECM graded 0–3, respectively

<table>
<thead>
<tr>
<th>Data cellular stages</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autophagic cell death (%)</td>
<td>25.9 ± 2.6 (51 fields)</td>
<td>42.9 ± 1.8 (205 fields)</td>
<td>51.9 ± 2.5 (71 fields)</td>
<td>46.9 ± 1.8 (296 fields)</td>
</tr>
<tr>
<td>Apoptotic cell death (%)</td>
<td>21 ± 2.2 (51 fields)</td>
<td>28.8 ± 1.8 (227 fields)</td>
<td>31.9 ± 2.1 (86 fields)</td>
<td>34.8 ± 1.6 (238 fields)</td>
</tr>
<tr>
<td>Myofibroblastic (%)</td>
<td>6.7 ± 1.3 (51 fields)</td>
<td>11.7 ± 0.9 (225 fields)</td>
<td>13.8 ± 1.0 (75 fields)</td>
<td>15.9 ± 1.2 (264 fields)</td>
</tr>
<tr>
<td>Cell density (cellular/mm²)</td>
<td>555 ± 4.1 (51 fields)</td>
<td>874 ± 21 (248 fields)</td>
<td>529 ± 17 (158 fields)</td>
<td>805 ± 17 (294 fields)</td>
</tr>
</tbody>
</table>

All the data were presented as mean ± SEM.
Degenerative changes of tendinopathy – reduction of functional tendon cell pool

• Apoptosis and autophagic cell death has been implicated in tendinopathies throughout the body

  • **Common Extensor Origin**
    • Chen et al, 2010; Kahlenburg et al, 2015

  • **Rotator cuff**
    • Yuan et al, 2002;
    • Tuoheti et al, 2005;
    • Millar et al, 2009;
    • Wu et al, 2011;
    • Lundgreen et al, 2011;
    • Lundgreen et al, 2013;
    • DeGiorgi et al, 2014

  • **Achilles**
    • Pearce et al, 2009; Nell et al, 2012; Wang et al, 2015

  • **Patellar tendon**
    • Andarawis-Puri et al, 2014; Lian et al, 2007
Biphasic effect of mechanical loading on tendon

![Graph showing cell apoptosis rate with different conditions: Native Control, 0% 6D, 0% 12D, 0%6D+6%6D.](image)

![Images of tissue samples under 10X and 40X magnification showing the effects of different mechanical loads: Uni-axial tension, Shear force, Compression.](image)
Tendon Loading

• Tendon is a mechanosensitive tissue in which the anabolic action of uni-axial loading only occurs in a narrow range at 6%.

• Mechanical loading deprivation and overloading always produce negative impacts on tendon structure.
Effect of Mechanical Loading on Tendon

Chester et al. 2008  Manual Therapy
Treatment Principle and Algorithm of Tendinopathy

Pathogenesis | Treatment principle
---|---
Overuse | Avoid re-injury
Angiofibroblastic hyperplasia | Mechanical induction of intrinsic repair
Degenerative change of tendon cell & matrix | Control of pain
Matrix breakdown & Fatigue healing | Substitution of tendon progenitor cells for tendon repair
Structural changes with mechanical failure | Correction of biomechanics & decompression

Rest | Physiotherapy | Injection | Cell | Surgery

Non-surgical treatment options - clinical evidence?

• Rest
• Bracing
• Physiotherapy
• Corticosteroid Injection,
• Botulinum Toxin A
• Laser
• Shockwave therapy
• Autologous Blood Injection
• PRP
• ATI ?
ATI Procedure

Biopsy

Starting tissue

GMP cell culture

Injection
Tendon Repair Process

Ultrasound guided injection of the patient’s own tendon progenitor stem cells (TPSC) into the site of tendinopathy / tear

Injected tendon progenitor stem cells infuse into the void within the tendon pathology
Tendon Repair Process

Tendon progenitor stem cells matrix integration

Tendon progenitor stem cells begin to produce tendon matrix, including type 1 collagen, in combination with appropriate mechanical stimulation.

Healing of tendon tissue by injected tendon progenitor stem cells

Healing of tendon tissue by injected tendon progenitor stem cells
Orthopaedic Journal of Sports Medicine 2017

Autologous Tenocyte Injection for the Treatment of Severe, Chronic Resistant Lateral Epicondylitis

A Pilot Study

Allan Wang,† MBBS, PhD, William Breidahl,‡ MBBS, Katherine E. Mackie,§ PhD, Zhen Lin,¶ An Qin,‖ PhD, Jimin Chen,¶ MD, PhD, and Ming H. Zheng,¶ DM, PhD

Investigation performed at Sir Charles Gairdner Hospital, Nedlands, Western Australia, Aus

The American Journal of Sports Medicine 2015

Evidence for the Durability of Autologous Tenocyte Injection for Treatment of Chronic Resistant Lateral Epicondylitis

Mean 4.5-Year Clinical Follow-up

Allan Wang,† MBBS, PhD, FRACS, Katherine Mackie,† PhD, William Breidahl,‡ MBBS, MRCP, FRANZCR, Tao Wang,† PhD, and Ming H. Zheng,¶ MD, PhD, FRCPath, FRCPA

Investigation performed at Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia


Lateral Elbow Tendinopathy

Development of a Pathophysiology-Based Treatment Algorithm

Gev Bhabra,† MD, FRACS(Orth), Allan Wang,‡ FRACS, PhD, Jay R. Ebert,§ PhD, Peter Edwards,§ BSc, Monica Zheng,‖ BPodM, and Ming H. Zheng,¶ PhD, MD, FRCPath

Investigation performed at Sir Charles Gairdner Hospital and University of Western Australia, Perth, Australia
ATI for Chronic LET
- Pilot Study -

- Safety, tolerability and evidence of efficacy study
- 17 patients with severe recalcitrant LET

<table>
<thead>
<tr>
<th>Table 1. Patient Demographics</th>
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<tbody>
<tr>
<td>Number of patients</td>
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<tr>
<td>Age ± SD (years)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Average duration of symptoms (months)</td>
</tr>
<tr>
<td>Length of follow-up (months) †</td>
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</tbody>
</table>
Outcome Measures

- Clinical (pre-, 1mth, 2mths, 3mths, 6mths, 1yr & 4.5yr)
- Disabilities of the Arm, Shoulder & Hand (QuickDASH)
- Upper Extremity Functional Score
- VAS Pain
- Grip Strength
- MRI (pre-, 1yr & 4.5yr)
MRI Outcomes
MRI Changes

Pre-ATI

- advanced common extensor tendinopathy
- partial thickness tearing of the deep (ECRB) portion

12mo post-ATI

- reduction in tendinopathy severity
- low grade partial thickness tearing remains, though significantly diminished
Summary

• Patients can tolerate the biopsy & injection;
• Continued clinical & MRI improvement to 12 mths, maintained at 4.5yrs
• Indications of efficacy - significant positive changes from baseline data, almost comparable to those who had surgery
• Limitations: small cohort, lack of comparative cohort
AUTOLOGOUS TENOCYTE INJECTION FOR THE TREATMENT OF COMPENSATING OCCUPATIONALLY RELATED LATERAL EPICONDYLITIS: A RETROSPECTIVE CASE STUDY

A O’Beirne, J Hughes, M Cannon, MH Zheng

1. The University of Western Australia, Crawley, WA 2. St John of God Hospital, Subiaco, WA 3. North Shore Private Hospital, St Leonards, NSW 4. Orthocell Ltd, Murdoch, WA

Background and Aims: Lateral epicondylitis (LE) is one of the common work related injuries. Sixteen per cent of patients with LE require work restrictions and frequently (4-5%) need prolonged absences from work, with a median 29 days missed per patient (1, 2). LE represents a significant socio-economic burden due to losses in individual productivity and health care costs. Autologous tenocyte injection (ATI) has recently been developed for the treatment of LE in patients who have failed for other conservative treatments. The objective of this study is to investigate if worker compensation patients with LE are able to return to their work after ATI treatment.

Methods: Retrospective case review on 25 patients (12 M / 13 F; mean age 49 years) was conducted. All of the patients were recorded for their medical history relating to the treatment of LE and capacity to return to work following autologous tenocyte injection.

Results: All patients presented with symptoms of on-going pain and dysfunction, which compromised their ability to participate in work and leisure activities. Patients were subject to restriction of duties for an average of 90.7 days per patient as a result of their tendon injury. There
Ortho-ATI™ in work-related common extensor tendinopathy

• Retrospective case review on 25 patients (12 M / 13 F; mean age 49 years).

• Evaluation of medical history relevant to the treatment of common extensor tendinopathy and capacity to return to work following Ortho-ATI™.

• Restriction of duties average 90.7 days per patient.

• Average absence from work of 64 days.

• Persistence of symptoms for an average of 22 months (±16.6) prior to treatment with Ortho-ATI™.
Indications for ATI

1) Positive MRI for tendinopathy.

2) Well localised tenderness.

3) Positive clinical provocation findings.
   • Failure of other conservative treatments;
   • Failure of symptoms to progress towards a level that are acceptable for the patient’s needs.
Indications for ATI

• Minimum 6 month unresolved symptoms.

• Failure to respond to conservative measures.

  OR

  • Failure to respond to surgery despite healing of tendon repair.

  OR

• Multiple sites of tendinopathy.
  • (surgical intervention is inappropriate).
Significant Prior Treatments

- 56% of patients
- Up to 8 prior treatments
Post Ortho-ATI™

- 3 – 6 months - pain reduced 90% at rest; 54% with use.
- Rapid return to work (1 – 3 months).
- 84% of patients failed prior treatments.
- 88% of patients returned to work post Ortho-ATI™.
- >50% returned at full capacity.
Greater Trochanteric Pain Syndrome (GTPS)

• 10-25% of the general population (Lievense, 2005; Segal, 2007; Williams, 2009)

• Includes trochanteric bursitis, external snapping hip, gluteal tendinopathy (GT) &/or tears

• Current treatment methods for GT include physical therapy, corticosteroids, anti-inflammatories, hot/cold treatment, SWT, PRP etc.

• Often symptoms linger and high reoccurrence rates exist, esp. after corticosteroids (Del Buono, 2012)
ATI Pilot Trial

- Patients -

- 12 females
- Mean age 53 yrs (range, 41-65)
- Mean DOS 30 months (range, 6-144)
- Mean corticosteroid injections 3 (range, 2-5)
- All patients underwent ‘failed’ physical therapy
Aim

• To investigate the safety & efficacy of Autologous Tenocyte Injection (ATI) in patients with clinical and radiological evidence of gluteal tendinopathy, who had failed other previous non-surgical treatments
ATI Pilot Trial
- Outcome Measures -

- Pre-injection & at 3, 6, 12 & 24 mths post-injection
  - VAS
  - Oxford Hip score
  - SF-36
  - Patient Satisfaction
- MRI at 6 mths
- All patients clinically reviewed by independent clinician
ATI – Gluteal Tendinopathy 2 Year Data
Pilot Trial

- Mean improvement of 14.9 points (95%CI: 10.6 – 19.2, p<0.001)
- 7/12 demonstrated a clinically important change of 11 or more points
ATI – Gluteal Tendinopathy 2 Year Data
Summary

• ATI has demonstrated significant clinical improvement for recalcitrant GT to 12 months, maintained at 24 months

• Invasive (but non-operative) intervention safe & well tolerated

• Encouraging early outcomes warrant further investigation
Conclusion

• Tendinopathy and tearing are caused by the depletion of tendocytes and breakdown of collagen matrix;

• Tenocytes are the ideal cell source for the substitution of tendon repair;

• Tenocytes can produce growth factors, form neo-tendon tissue, integrating into tendon matrix;

• Phase I clinical data of ATI is promising.
Treatment Principle and Algorithm of Tendinopathy

Pathogenesis | Treatment principle
---|---
Overuse | Avoid re-injury
Angiofibroblastic hyperplasia | Mechanical induction of intrinsic repair
Degenerative change of tendon cell & matrix | Control of pain
Matrix breakdown & Fatigue healing | Substitution of tendon progenitor cells for tendon repair
Structural changes with mechanical failure | Correction of biomechanics & decompression

Rest | Physiotherapy | Injection | Cell | Surgery

Tears at the rotator cuff footprint: Prevalence and imaging characteristics in 305 MR arthromgs of the shoulder

Christoph Schaeffeler · Dirk Mueller · Chlodwig Kirchhoff · Petra Wolf · Ernst J. Rummeny · Klaus Woertler

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Abstract

Objectives To evaluate the prevalence, imaging characteristics and anatomical distribution of tears at the rotator cuff (RC) footprint with MR arthrography (MR-A) of the shoulder.

Methods MR arthromgs obtained in 305 patients were retrospectively reviewed. Partial articular-sided supraspinatus tendon avulsions (PASTA), concealed interstitial delaminations (CID), reverse PASTA lesions and full-thickness tears (FT) at the humeral tendon insertion were depicted. Anatomical locations were determined and depths of tears were classified.

Results 142/305 patients showed RC tear including 62
difference in anatomical location ($p=0.903$) and no correlation with overhead sports activity ($p=0.300$) or history of trauma ($p=0.928$). There were significantly more PASTA lesions in patients <40 years of age ($p=0.029$).

Conclusions Most RC tears detected with MR-A involve the SSP footprint and are articular-sided with predominance in younger patients, but concealed lesions are not as uncommon as previously thought.

Keywords Magnetic resonance imaging · Arthrography · Shoulder joint · Tendon injuries · Rotator cuff
Fig. 1. Drawings of the shoulder in the coronal oblique plane show different types of tendon tears at the rotator cuff footprint. 

a) Partial articular-sided supraspinatus (SSP) tendon avulsion (PASTA) lesion with tendon failure on the articular side. As shown on the drawing, an associated horizontal delamination of tendon fibres is possible. 

b) Concealed interstitial delamination (CID) lesion which is covered by intact tendon fibres on both the articular and the bursal side. 

c) Reverse PASTA lesion with a bursal-sided defect of the tendon, continuous to the subdeltoid bursa. 

d) Full-thickness tear with continuous extension of the defect from the joint space to the subdeltoid bursa.
Novel treatment (new drug/intervention; established drug/procedure in new situation)

Autologous tenocyte implantation, a novel treatment for partial-thickness rotator cuff tear and tendinopathy in an elite athlete

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SUMMARY
Tendinopathy and small partial-thickness tears of the rotator cuff tendon are common presentations in sports medicine. No promising treatment has yet been established. Corticosteroid injections may improve symptoms in the short term but do not primarily treat the tendon pathology. Ultrasound-guided autologous tenocyte implantation (ATI) is a novel bioengineered treatment approach for treating tendinopathy. We report the first clinical case of ATI in a 20-year-old elite gymnast with a rotator cuff tendon injury. The patient presented with 12 months of increasing pain during gymnastics being unable to perform most skills. At 1 year after ATI the patient reported substantial improvement of clinical symptoms. Pretreatment and to the initial presentation. There was no specific trauma, but symptoms were gradually progressive despite physiotherapy. In April 2011, the pain had become more severe. The athlete described the symptoms as moderate pain in the left shoulder when supporting the entire bodyweight on his arms and severe when hanging and swinging from his arms at full extension on rings and parallel bars. No night pain was experienced. In June 2011, a subacromial corticosteroid injection became necessary to enable the athlete to participate at national championships. However, shoulder symptoms recurred and precluded continuation of regular training sessions.

INVESTIGATIONS,
MRI – BMJ case report
Take home message

• Tendon needs a sweet spot for mechanical stimulation

• Early studies indicate that ATI has a useful role in the treatment of chronic recalcitrant tendinopathy i.e. stage 3 and stage 4 disease.

• Not one size fits all. Consider treatment algorithm.
THANK YOU

Dr K A Rao Annual Scientific Meeting ANZSOM
Fremantle August 2017
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