What Internists Need To Know About Common Orthopedic Problems: Focus on Tendinopathy
I have no relevant financial or non-financial relationships to disclose.
Why Tendinopathy?

“Good news.
Your cholesterol has stayed the same, but the research findings have changed.”
Objectives

- Review the epidemiology, pathophysiology, and diagnosis of tendinopathy

- Discuss evolving management strategies of tendinopathy

- Develop an updated algorithm to approach diagnosis and management of tendinopathy
Introduction

- Overview of the tendon
  - Dense connective tissue, connecting muscle to bone

- Structure dependent on interplay of:
  - Extracellular matrix
    - Composed of parallel collagen (type I) fibers
  - Local cell types
    - Tenocytes: produce ECM components for growth/healing
    - Tenoblasts: capable of differentiating into tenocytes
    - Tendon stem cells

- Tissue strength » ability of collagen molecules to form an organized and cross-linked structure

Epidemiology

Among the most common overuse injuries

~30% of GP MSK consultations are for tendinopathy
- Up to 30-50% of sporting injuries involve tendinopathy
- Prevalence up to 41% reported in certain occupations

Resultant disability
- Full recovery can require 10-12 months
- One study suggested that up to 5% of patients with LE claim sickness absence of ~29 days in a year

Introduction

- Common sites of tendon injury
  - Rotator cuff
  - Lateral elbow/common extensor bundle
  - Patellar tendon
  - Achilles tendon
  - Biceps tendon
  - Medial elbow/common flexor bundle
  - Hamstring tendon
  - Gluteus medius/minimus tendons
  - Posterior tibialis tendon

What’s in a name?

- **Greater trochanteric bursitis**
  - Classically described pain originating from the lateral hip
  - Very common (10-25% of general population; 18-45% with LBP)
  - Bursitis likely plays small role in lateral hip pain (Bird, 2001)
    - 24 women with lateral hip pain
    - 2 (8.3%) had radiographic findings of bursitis
    - 63% with gluteus medius tendinitis; 46% with gluteus medius tear
  - **Gluteal tendon pathology** = most common cause of greater trochanteric pain
    - Gluteus medius
    - Gluteus minimus

“Greater Trochanteric Pain Syndrome”

Introduction

- Spectrum of tendon injury
  - Acute tendon **rupture**
  - **Tendinopathy**: clinical syndrome of pain and reduced tendon function
    - **Tendinitis**: histopathologic evidence of inflammation
    - **Tendinosis**: minimal inflammation, degenerative changes

Pathophysiology

**Repetitive Tendon Load**

- **Microscopic tendon fiber damage**
  - Damage to collagen fibrils, non-collagenous matrix, microvasculature

- **Inflammation and local tissue hypoxia**
  - Tissue edema, fibrin exudate, capillary occlusion

- **Disordered tendon tissue (thickening of tendon/paratenon)**
  - Fibroblast proliferation and fibrotic adhesions

- **Tendon degeneration**
  - Ongoing hypoxia, free-radical release, cell apoptosis

Tenon injury is often **multifactorial**

### Extrinsic Risk Factors
Circumstances external to or independent of the individual

- Overuse
- Sports participation (type of sport, training errors)
- Occupational exposure including environment and ergonomics
- Medications (eg fluoroquinolones)

### Intrinsic Risk Factors
Traits specific to an individual and the way the body assumes stress

- Advancing age
- Anatomical abnormalities
- Biomechanics
- Systemic disorders (eg diabetes, inflammatory conditions)
Diagnosis is often clinical

- History
  - Insidious onset of pain
  - Pain worse with inciting activities

- Physical exam
  - Pain to direct palpation
  - Passive stretch of the muscle-tendon unit
  - Resisted activation of the muscle-tendon unit
  - Tendon thickening (palpation, impingement)
  - Mechanical deficits elsewhere in the kinetic chain
Diagnosis

- Imaging
  - Advanced imaging may help to confirm diagnosis
    - MRI or ultrasound
  - When to consider advanced imaging:
    - Appreciable weakness on exam
    - Rule out more sinister diagnosis
    - Failure to improve with appropriate conservative care
Treatment

- Goals of management:
  1. Pain reduction
  2. Tendon recovery and repair
  3. Return to pre-injury function
  4. Recurrence prevention
Development of tendinopathy is multifactorial

- Envelope of function
Identify and address *modifiable risk factors*

**Extrinsic Risk Factors**
Circumstances external to or independent of the individual

- Overuse
- Sports participation (type of sport, training errors)
- Occupational exposure including environment and ergonomics
- Medications (e.g., antibiotics)

**Intrinsic Risk Factors**
Traits specific to an individual and the way the body assumes stress

- Advancing age
- Anatomical abnormalities
- Biomechanics
- Systemic disorders (e.g., diabetes, inflammatory conditions)
Activity modification

- Load management = cornerstone of treatment
  - Especially important for those engaging in repetitive stress/loading activities (sport, work)

- Limit volume and intensity of load
  - Avoid activities that worsen pain
  - Complete immobilization typically not indicated
    - Immobilization can be detrimental to healing
      - Reduced production of extracellular matrix → decreased structural properties of repair tissue

- Passive motion = ideal loading environment for healing

Treatment

- Activity modification

- Activity allowable if pain ≤5:
  - During activity
  - After completion of activity
  - The morning after activity

- Pain/stiffness should not increase from week to week

Physical therapy

- Supervised exercise program
  - Graduated loading activities
  - Isometric contractions (early/painful stages)
    - Avoid positions that compress tendon insertion
  - Isotonic resisted exercises (once adequate strength achieved)
    - Emphasis on *eccentric strengthening*
  - Progressive sport-specific exercise
    - Consider biomechanical analysis (e.g. gait, throwing) and/or ergonomic evaluation

What next?
Anti-Inflammatory versus Pro-Inflammatory

- Traditional approach to musculoskeletal care focused on limiting inflammation
  - Reduce pain and facilitate rehabilitation

- Paradigm shift
  - Many musculoskeletal conditions (including tendinosis) demonstrate limited inflammation histologically
    - Rather, represent tissue degeneration and/or suboptimal healing response
  - Anti-inflammatories do not facilitate tissue healing
  - Rising concern that reducing inflammatory response may impair healing
Corticosteroid and Tendon Healing

- Controlled laboratory study (Beitzel, 2013)
  - Chondrocytes and tenocytes from human LHBT
    - In culture w/ ketorolac, methylprednisolone, and/or PRP
    - Control: treated in 2% and 10% fetal bovine serum (FBS)
  - Outcomes: cell viability at 24 hr and 120 hr
  - Results:

Tenocytes

Corticosteroid and Tendon Healing

- **RCT (Coombes, 2013)**
  - 165 patients with lateral epicondylitis (LE) > 6 wks
  - Randomized to:
    - Steroid injxn (n=43) vs Steroid injxn + PT (n=40)
    - Saline injxn (n=41) vs Saline injxn + PT (n=41)
  - Outcomes: improvement rating (4, 26, 52 wk); relapse (1 yr)

- **Results:**
  - Significant Improvement at 4 weeks
  - Recurrence at 52 weeks

Which Way?

Anti-Inflammatory →

Pro-Inflammatory ←
Phases of Healing

**Inflammation**

- **Hemostasis**
  - Coagulation cascade
  - Platelet aggregation
  - Release of cytokines and growth factors (TGF, PDGF, VEGF)

- **Inflammation**
  - Accumulation of prostaglandins and leukotrienes → attract neutrophils

- **Phagocytosis**
  - Influx of macrophages → nitric oxide and MMPs

**Proliferation**

- **Angiogenesis**
  - VEGF attracts endothelial cells
  - Neovascularization

- **Fibroplasia**
  - PDGF and TNF-α stimulate fibroblasts
  - Synthesize collagen and provisional matrix

**Maturation**

- Strengthening of extracellular matrix
- Production of collagen into an organized network

Treatment

- Pro-inflammatory approaches
  - Topical glyceryl trinitrate (GTN)
  - Prolotherapy
  - Platelet rich plasma (PRP)
  - Dry needling
  - Autologous blood
  - Extracorporeal shockwave therapy (ESWT)
  - Ultrasound therapy
  - Laser therapy
Treatment

- Topical glyceryl trinitrate (GTN)
  - Delivers nitric oxide locally →
    - Increases local blood flow
    - Promotes collagen synthesis

**Hemostasis**
- Coagulation cascade
- Platelet aggregation
- Release of cytokines and growth factors (TGF, PDGF, VEGF)

**Inflammation**
- Accumulation of prostaglandins and leukotrienes → attract neutrophils

**Phagocytosis**
- Influx of macrophages → nitric oxide and MMPs

**Angiogenesis**
- VEGF attracts endothelial cells
- Neovascularization
- PDGF and TNF-α stim fibroblasts
- Synthesize collagen and provisional matrix

**Strengthening of extracellular matrix**

**Production of collagen into an organized network**

Challoumas D, et al. BMJ. 2018 (epub ahead of date)
Topical glycercyl trinitrate (GTN)

RCT (Paoloni, 2003)

- 86 patients with lateral epicondylosis
- Randomized to GTN (n=43) or placebo (n=43) + HEP

Results:

- GTN improved early pain and late functional measures

### Treatment

- **Topical glyceryl trinitrate (GTN)**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Type of tendinopathy</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paoloni, 2003</td>
<td>Common extensor</td>
<td>Yes</td>
</tr>
<tr>
<td>Paoloni, 2009</td>
<td>Common extensor</td>
<td>Yes</td>
</tr>
<tr>
<td>Ozden, 2014</td>
<td>Common extensor</td>
<td>Yes</td>
</tr>
<tr>
<td>Paoloni, 2004</td>
<td>Achilles</td>
<td>Yes</td>
</tr>
<tr>
<td>Kane, 2008</td>
<td>Achilles</td>
<td>No</td>
</tr>
<tr>
<td>Paoloni, 2005</td>
<td>Rotator cuff</td>
<td>Yes</td>
</tr>
<tr>
<td>Giner-Pascual, 2011</td>
<td>Rotator cuff</td>
<td>Yes</td>
</tr>
<tr>
<td>Steunebrink, 2013</td>
<td>Patellar</td>
<td>No</td>
</tr>
</tbody>
</table>

- **Some considerations**
  - Relatively small sample sizes (33-154)
  - Small changes in pain scores (?clinical significance)
  - Single author/group reporting majority of outcomes
  - High reporting bias
Treatment

- **Topical glyceryl trinitrate (GTN)**

**Conclusion**

The results of this review provide good evidence for the effectiveness of GTN in the short and intermediate term treatment of tendinopathies (<6 months). GTN treatment is thus a good example that translational tendinopathy (laboratory bench to patient) can provide pharmacological adjuncts to aid the practising healthcare professional in addition to loading regimes. Importantly, other than headaches and occasionally rashes, topical GTN is a safe and practical treatment modality with very low costs both for the patient and the healthcare system. Therefore, the use of topical GTN should be considered for all chronic tendinopathies as an adjunct to loading programmes that fail to produce satisfactory resolution of symptoms. However, physicians should alert patients that large, well-designed RCTs and prospective cohort studies are warranted to provide convincing evidence on the effects of topical GTN in both acute and chronic tendinopathy, especially its long-term outcomes.
Treatment

- **Topical glyceryl trinitrate (GTN)**
  - **Practical use**
    - **Dose**: 0.72 – 2.5 mg/day (typical dose = 1.25mg/day)
      - Patch applied to point of maximal tenderness
      - Change patch every 24 hours
    - **Duration**: 8 – 24 weeks
  - **Side effects**
    - Hypotension, dizziness
    - Headache (in up to 1 of 5 patients)
    - Rash
Treatment

- Platelet rich plasma (PRP)
  - Portion of plasma from autologous blood having platelet concentration above baseline
  - Application in musculoskeletal medicine
    - Platelets release growth factors

<table>
<thead>
<tr>
<th>Hemostasis</th>
<th>Angiogenesis</th>
<th>Strengthening of extracellular matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation cascade Platelet aggregation</td>
<td>- VEGF attracts endothelial cells</td>
<td>Production of collagen into an organized network</td>
</tr>
<tr>
<td>Release of cytokines and growth factors (TGF, PDGF, VEGF)</td>
<td>- Neovascularization</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td>Fibroplasia</td>
<td></td>
</tr>
<tr>
<td>Accumulation of prostaglandins and leukotrienes → attract neutrophils</td>
<td>- PDGF and TNF-α stim fibroblasts</td>
<td></td>
</tr>
<tr>
<td>Phagocytosis</td>
<td></td>
<td>Synthesize collagen and provisional matrix</td>
</tr>
<tr>
<td>Influx of macrophages → nitric oxide and MMPs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment

- **Platelet rich plasma (PRP)**
  - **Derivation**

![Diagram of blood separation process](image)

- Whole Blood
- Centrifuge
- Plasma
- WBCs (Buffy coat)
- RBCs
Treatment

- Platelet rich plasma in the press
Platelet rich plasma (PRP)

- Systematic review (Filardo, 2016)
  - 92 studies dealing w/ application of PRP for tendinopathy
    - Patellar (19), Achilles (24), lateral elbow (29) and/or RTC (32)

- Patellar tendinopathy
  - PRP seems to be associated with clinical benefit

- Achilles tendinopathy
  - PRP not indicated as conservative approach/surgical augmentation

- Lateral elbow tendinopathy
  - PRP associated with improvement in most high-level studies

- Rotator cuff pathology
  - Majority of surgical RCTs lack beneficial effects
  - Inconclusive evidence concerning conservative application

Platelet rich plasma (PRP)

- The available evidence base for assessing the effects of platelet-rich therapies for treating musculoskeletal soft tissue injuries comprises a diverse collection of small trials...
- There is very low quality evidence from a subset of these trials for a marginal short-term benefit in pain
- However, other very low quality indicates no clear relevant effect on short- or long-term function

Moraes VY, Lenza M, Tamaoki MJ, Faloppa F, Belloti JC

Moraes VY, et al. Cochrane Database of Systematic Reviews 2014, Issue 4
Treatment

- Platelet rich plasma (PRP)
  - Limitations in literature and current knowledge
    - PRP preparation
      - Ideal platelet concentration
      - Leukocyte-rich versus leukocyte-poor
      - Platelet activation by exogenous agents
      - Red blood cell presence/concentration
    - Injection procedure
      - Volume and frequency
      - Application of dry needling
      - Use of image guidance
      - Use of anesthetic
    - Post-procedure protocol and rehabilitation

Platelet rich plasma (PRP)

**Practical use**
- Performed in clinic at the bedside
  - Phlebotomy (retrieve ~15cc whole blood)
  - Centrifuge and extraction of PRP
  - Injection to area of disease (often under image guidance)

**Post-procedure precautions**
- Avoid anti-inflammatories (ice, NSAIDs, etc.)
- Activity modification ± offloading for 1-4 weeks

**Side effects**
- Bleeding, infection, increased pain, etc. (minimal risk)
- **Cost $$$$$**
Treatment

- **Extracorporeal shockwave therapy (ESWT)**
  - Electromagnetic or pneumatic device produces:
    - Abrupt, high amplitude soundwaves/pulses mechanical energy
  - Microtrauma generates inflammatory response:
    - Promotes neovascularization, increases leukocyte infiltration and growth factor synthesis

<table>
<thead>
<tr>
<th>Hemostasis</th>
<th>Angiogenesis</th>
<th>Strengthening of extracellular matrix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulation cascade Platelet aggregation</td>
<td>VEGF attracts endothelial cells</td>
<td>Production of collagen into an organized network</td>
</tr>
<tr>
<td>Release of cytokines and growth factors (TGF, PDGF, VEGF)</td>
<td>Neovascularization</td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accumulation of prostaglandins and leukotrienes → attract neutrophils</td>
<td>PDGF and TNF-α stim fibroblasts</td>
<td></td>
</tr>
<tr>
<td>Phagocytosis</td>
<td>Synthesize collagen and provisional matrix</td>
<td></td>
</tr>
<tr>
<td>Influx of macrophages → nitric oxide and MMPs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment

- Extracorporeal shockwave therapy (ESWT)
  - Retrospective cohort (Carulli, 2016)
    - 311 patients with tendinopathy
      - RTC calcific tendinitis (n=129), Achilles (n=102), LE (n=80)
      - Clinical measures at 1, 6, and 12 months
  - Results

Treatment

- Extracorporeal shockwave therapy (ESWT)
  - Retrospective cohort (Carulli, 2016)

Results

Extracorporeal shockwave therapy (ESWT)

Practical use:
- Dose: 1500-3000 pulses, EFD 0.04-0.28 mJ/mm²
  - EFD = energy per impulse at focal point of shockwave
- Frequency: weekly
- Duration: 3-4 sessions
- Avoid concomitant anti-inflammatory agents

Side effects
- Pain, redness, swelling, minor bruising
- Skin erosion, tendon rupture, bone injury (rare)
Approach to Treatment

Adapted from:
Approach to Treatment

- **Step 1: activity modification and physical therapy**
  - Avoid complete immobilization
  - Progressive eccentric exercise
  - Biomechanical and/or ergonomic assessment

- **Step 2: trial of anti-inflammatories (NSAIDs, ? steroid injxn)**
  - Corticosteroid injection contraindicated for:
    - Achilles tendon, patellar tendon, posterior tibialis tendon
    - Evidence of tendon tear (relative)

- **Step 3: advanced imaging (e.g. MRI)**

- **Step 4: topical glyceryl trinitrate or ESWT**

- **Step 5: discuss PRP, consider surgical referral**
Summary

- **Tendinopathy is a common clinical problem**
  - Development is multifactorial
  - Diagnosis is clinical
    - Advanced imaging considered in refractory cases
  - Occurs along a spectrum
    - Initial inflammatory response
    - Disordered tendon tissue and degeneration

- **Management of tendinopathy**
  - Load management and PT represent cornerstone
  - Trial of anti-inflammatory is often appropriate
  - Consider pro-inflammatory approach in refractory cases
References


Challoumas D, et al. BMJ. 2018 (epub ahead of date)


Moraes VY, et al. Cochrane Database of Systematic Reviews 2014, Issue 4


