What in tendinopathy?
Muscular force (pedal) - Movement (wheel)

Muscle contraction - Tendon

MTJ – Myotendinous junction
IMCT - Intramuscular connective tissue
Tendinopathy - What can we agree upon?

Repetitive stress (i.e. too much training intensity or volume) that involves the tendon elastic function and results in tendon related symptoms

Clinical
Pain and dysfunction of tendon
What is tendinopathy - What can we agree upon?

**Clinical**
- Pain with activity
- Tenderness upon palpation
- Swelling of tendon
- Impaired performance

**Structure - Imaging (US or MRI)**
- Thickening of tendon
- Hypoechoic tendon areas (US)
- Altered water content
- Hyperperfusion

**Morphology - Histology**
- Cell rounding and reduced number
- Disorganized collagen fibrils
- Fibrils smaller and looser organized
- Accum. of proteoglycans, GAG’s and water
- Vascular growth - angiogenesis


Tendinopathy

Healthy Tendinopathy

From perfect function to painfull, impaired activity

**CLINICAL**
- Decreased performance
- Swelling
- Pain
- Soreness
- Blood flow

**BASIC**
- Morphology altered (disalignment, low cell no.)
- Biochemical changes (proteoglycans, water)
- Nociceptive subst.
- Vascularity altered

From physiology to pathology
Tendinopathy pathogenesis

- Mechanical damage – acute healing response
- Mechanical damage – "shielding off"
- Microdamage – inflammatory response
- Immune response – vasculature permeability
- Peripheral neural phenotype – primary adrenergic stimulation
- Primary breakdown – metalloproteinase activity
- Proteoglycan metabolism perturbation
- Homeostasis perturbation – constant overload, apoptosis
- Hypoxia, oxidative stress - hypervascularity, nerve ingrowth
- Genetic predisposition
- Compressive overload
Mechanisms behind tendinopathy (1)

Mechanical damage to tendon region – loading larger than tolerable. Acute healing response – Regeneration of tissue

**PRO:** Fibroblast proliferation, angiogenesis, nerve ingrowth

**CONTRA:** No visualized lesion, biochemical profile not like rupture


Shielding off – theory, Minor mechanical damage followed by region unloading

**PRO:** Localized region, slow loading effective as treatment, fibrils in tendon

**CONTRA:** Difficult to demonstrate the ”shielding”, sudden onset

(Arnozky 2009)

Inflammatory response to microdamage

**PRO:** Early event, HSP+pro-infl.markers, respons to anti-inflammatory treatment

**CONTRA:** Histological degeneration, no ”inducable” inflamm. in chronic state

(Fredberg 2008, Murrell 2010, Pingel 2013)
Mechanisms behind tendinopathy (2)

Proteoglycan metabolism perturbation
PRO: Thickening of tendon
CONTRA: Primary or secondary event
(Caterson 2010)

Hypoxia, oxidative stress – little vasculature, hypervascularity, nerve ingrowth
PRO: Less vasculature and rupture, HIF in rotator cuff, apoptosis in tendon
CONTRA: No detectable hypoxia
(Boushel 2000, Millar 2009, Dean & Carr 2014)

Peripheral neuronal phenotype – Primary neuronal and adrenergic stimulation
PRO: Early nociceptors and neuronal activity, accellerated ”exagerated” pain,
CONTRA: Difficult to detect early
(Dean 2013, Ackermann 2009, Danielson 2007, Forsgren 2009)
Primary breakdown of tendon tissue – activation of matrix metalloproteinases
PRO: Altered structure of matrix
CONTRA: Collagenase model, not detectable in humans
(Sun 2008, Orchard 2008)

Constant overload on tendon “work horse” cells – less synthesis, more degradation. Accumulation of tissue between fasicles
PRO: Synthesis and degradation increased with exercise, recovery
CONTRA: Link to pathology lacking
(Miller 2005, Magnusson 2010, Heinemeier 2013)
Mechanisms behind tendinopathy (4):

**Compressive load induced tendinopathy**
**PRO:** Compression points, collagen II+aggrecan formation, fibrocartilage finding, rounded cells  
**CONTRA:** Other locations than enthesopathy, other histological findings  

**Immune response – vasculature permeability to innate immune system**
**PRO:** Permeable vessels, oxidative stress, few immunocomp. cells in tendon  
**CONTRA:** No in vivo detection of response  
(Tempfer/Bauer 2009,2011)

**Genetic factors determine who will be injured**
**PRO:** Correlates to polymorphism in e.g. Collagen V  
**CONTRA:** Overruled by many other things  
(Collins 2010)
Mechanisms behind tendinopathy – where are we?
"The 3 most likely mechanisms....out of many”

Mechanical damage to tendon region ("a small partial rupture").
Inflammation, regeneration and healing response, Shielding off

Constant overload on tendon cells ("disturbed homeostasis").
Interfascicular cell-tissue disturbance, fibril fragments.

Compressive load ("altered connective tissue")
Fibrocartilagenous changes at insertional points, hypoxia
Mechanical damage to tendon region ("a small partial rupture"). Inflammation, regeneration and healing response, Shielding off

Fibroblast proliferation, angiogenesis, nerve ingrowth (+)
Early (but not late) presence of inflammation (+)
Localized area – "shielded off?" (+/-)
No convincing imaging technique has demonstrated fibril damage (-)
No increased rupture risk (-)

Proteolytic signalling (MMP) in tendinopathy

Different mRNA profile in tendinopathy and tendon rupture (-)

Matrix metalloproteinase (MMP)

Mechanisms behind tendinopathy – where are we?
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Compressive load (”altered connective tissue”)
Fibrocartilagenous changes at insertional points, hypoxia
Mechanical loading of tendon:

Collagen in fibrils/fascicles – no turnover
(95% stable structures after adolescence)

High turnover Collagen
(5% - fibril fragments inter-fascicular?)

Non-collagenous matrix molecules
(Proteoglycans, a) large: aggrecan, versican
b) SLRP: decorin (80%), biglycan, lumican, fibromodulin)

COMP, Lubrican, Elastin, Tenascin-C, Fibronectin

Cross-links
(a) enzymatic: lysyl oxydase initiated, b) advanced
glycation endproducts (AGE’s))
Fibroblasts responsive to physiological loading?
“Daily work horses” – “between fascicles/outer layer”

1. Collagen fibril formation and adaptation is very dynamic in childhood/adolescence (large pool) – after that time the main structures (“wires”) are stable

2. Mechanical loading stimulates turnover in a small pool of collagen and cross-links that modifies mechanical properties

Tendon

Fibroblasts relatively “dormant” under normal conditions

(Heinemeier et al, FASEB J, 27: 2074-9, 2013)
Accumulation of matrix between fascicles?

Inter-fascicular space: Highly cellular, fibril fragments, vascular, nerves

(Haraldsson et al. Matrix Biol, 2007)
Tendon clock controls many genes

>745 rhythmic genes in tendon = potentially 745 biological processes

Matrix remodeling and inflammation related primarily to the inter-fascicular area

Collagen in fibrils/fascicles – no turnover (95% stable)
High turnover Collagen (5% - fibril fragments inter-fascicular?)

Bovine (cow) flexor tendons subjected to cyclic uniaxial loading (1-10% strain)

Non-uniform aponeurosis displacement result in shear forces between soleus and gastrocnemius of 3-4 mm

(Bojsen-Moller et al JAP 2004)
Mechanisms behind tendinopathy – where are we?
”The 3 most likely mechanisms....out of many”

Mechanical damage to tendon region (“a small partial rupture”). Inflammation, regeneration and healing response, Shielding off

Constant overload on tendon cells (“disturbed homeostasis”). Interfascicular cell-tissue disturbance, fibril fragments.

Compressive load (“altered connective tissue”) Fibrocartilagenous changes at insertional points, hypoxia
Achilles tendon insertion
Compressive load ("altered connective tissue")
Fibrocartilagenous changes at insertional points, hypoxia

(Benjamin personal communication)
Increased number of inflammatory cells are present in tendinopathic tendons - revival of ”tendinitis”?

Table 2  Inflammatory cells in tendinopathic specimens versus healthy control tendon

<table>
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<th>Cell marker</th>
<th>Cell type</th>
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<td>→,↑, ND</td>
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<td>B cell</td>
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<td>CD45</td>
<td>Leucocyte</td>
<td>→</td>
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<td>Natural killer cell</td>
<td>→</td>
<td>↑</td>
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<tr>
<td>CD68/CD206</td>
<td>Macrophage</td>
<td>↑, ND</td>
<td>↑</td>
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<tr>
<td>Mast cell trypate/NaSDCI</td>
<td>Mast cell</td>
<td>↑, →</td>
<td>↑</td>
</tr>
</tbody>
</table>

(Dean et al BJSM, 2015)
Inflammation activation and resolution in human tendon disease

Macrophages

Human supraspinatus/subscapularis tendon

Inflammation markers

(Science Transl Med, 2015)
Tendinopathy - What are the challenges?

20 years ago: ”Tendinitis”....to tendinopathy...”free choice” of treatment

10 years ago: Starting to get the treatments clinically investigated

Today: Starting to get the theories for tendinopathy pathogenesis tested

De facto challenges in the clinical-paraclinical-theoretical interface:

Mismatch between symptoms and imaging findings (e.g. flow)

Mismatch between tissue pathology and perceived pain

Mismatch between general tendon tissue changes (disorganized matrix, rounded cells) and specific regional presentations (anatomy), differential locations (insertion vs mid-substance) and variation in patient characteristics (e.g. age)

Not 100% effective treatment (Strength training around 75%), combinations?
We have a good idea of what tendinopathy is but we don't know for sure what the pathogenesis is.

When we try to treat tendinopathy, we need to consider what we think the etiology/pathogenesis and the presentation of the injury is.
Thank you:

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www.ismc.dk