Statin Use and Tendinopathies: Overview, Mechanisms, and Relevant Data

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References

Clinical question: Do tendinopathies pose any relative or absolute contraindications to statin therapies?

Background

- **Tendinopathies** are among the most frequent musculoskeletal complaints and tend to increase in our aging population
- This population is often prescribed statins to treat hypercholesterolemia, with at least 92 million users globally
- Statins stabilize coronary artery plaques and reduce the risk of myocardial infarction, stroke, and death from cardiovascular and atherosclerotic diseases.
- Risk of statin-induced serious muscle injury, including rhabdomyolysis, is <0.1%, while the risk of serious hepatotoxicity is approximately 0.001%.
- Use of statins ***may*** be associated with certain tendinopathies and tendon ruptures, especially of the Achilles, quadriceps, and distal biceps tendons.
- According to the American Heart Association, there is no good evidence to suggest that statins increase the risk of tendonitis or tendon rupture (based on the Teichtahl systematic review).
- Metalloproteinases (MMPs) are a group of enzymes that break down proteins in the extracellular matrix in collagen degradation

Case

55 year old male

- Past medical history: uncontrolled hypertension, elevated BMI (36), depression, hypercholesterolemia and multiple ankle musculoskeletal pathologies (tendonitis, tendinosis, tenosynovitis ankle ligament tears).

History of Present Illness

- Initially presented for consult to sports medicine for chronic right ankle pain.
- Underwent directed physical therapy without resolution of symptoms.
- MRI findings: Severe tendinosis and tenosynovitis of the posterior tibial tendon with extensive interstitial tear of the supramalleolar and inframalleolar portion, Peroneus longus tendinosis with anterolateral subluxation along the lateral margin of the fibula, Peroneus brevis tendinosis and longitudinal split tear, and anterior talofibular ligament tear.
- Patient had a follow-up appointment regarding chronic issues including essential hypertension and hypercholesterolemia.

Physical Exam

Ankle exam

- Progressive collapsing foot deformity, out-toeing
- Non tender to palpation over fibular head, lateral malleolus, achilles, navicular, base of 5th, Anterior talofibular ligament, Calcaneofibular Ligament, deltoid, calcaneus or midfoot
- Tender to palpation of the medial malleolus, posterior tibial tendon and Flexor digitorum longus tendon
- Range of motion: Dorsiflexion 30, Plantar Flexion 45, inversion and eversion intact
- Negative ant drawer, talar tilt, rotation test, squeeze test, thompson test.
- Pain with resisted inversion or eversion

Assessment

55-year-old male with past medical history of essential hypertension, elevated BMI 36, hypercholesterolemia with 10-year ASCVD risk score of 11.1%. With constellation of tendon pathologies, risk benefit discussion had with patient about statin therapy initiation.

Mechanisms

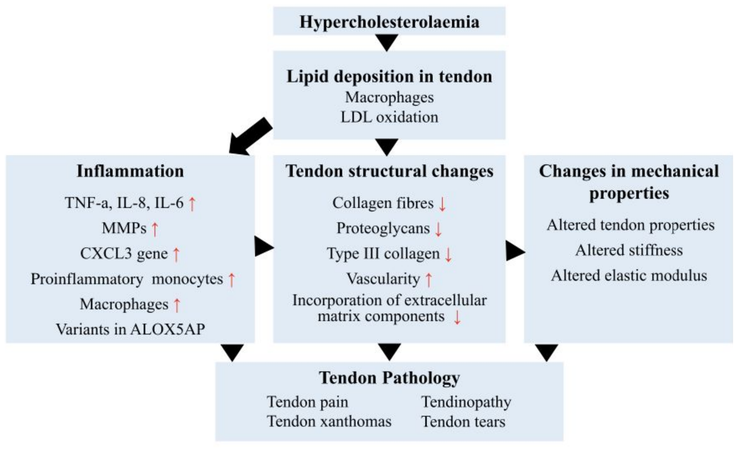

Figure 1. Hypercholesterolemia as a potential risk factor for tendinopathy
Yang et. al figure depicting pathogenic mechanisms of hypercholesterolemia on tendons. MMPs = matrix metalloproteinases; LDL = low-density lipoprotein; TNF-a = Tumor necrosis factor alpha; IL-8 = interleukin 8; IL-6 = interleukin 6.

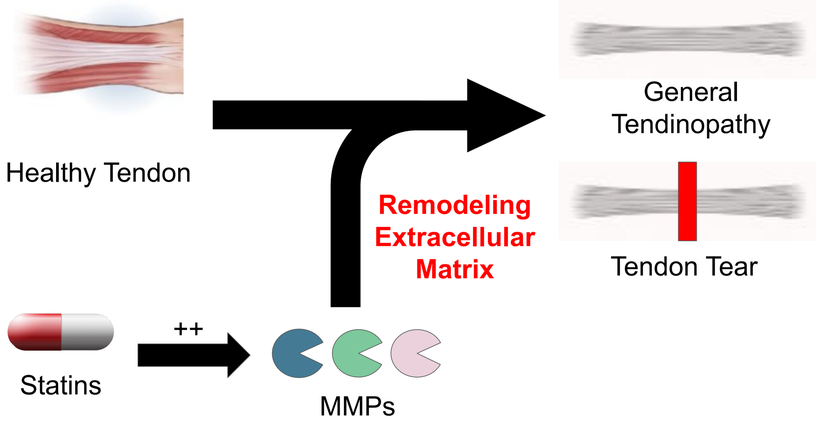

Figure 2. Statin-Induced Tendinopathy
Proposed mechanism of statin-induced tendinopathies through upregulation of Matrix Metalloproteinases which results in a weakened tendon matrix ultimately leading to tendinopathies.

Summary and Results from Relevant Published Studies

Statins and tendinopathy: a systematic review (2016) by Teichtahl et. al

Objective: Systematically review evidence on whether statins contribute to tendinopathy and examine causality using the Bradford Hill Criteria.

Study selection: Adult human studies published in English from January 1966 to October 2015. Eligible studies: RCTs, cross-sectional, cohort, or case-control studies.

Method/Data: 4 studies (3 cohort and 1 case-control). Primary outcome was tendon rupture and rotator cuff disease

Definitions: Statin exposure definition varied — use in the 12 months preceding tendon rupture, or statin use for >28 days

Table 2. Studies looking at Statin therapy associated with tendinopathies from Teichtahl et. al

Study	Design	Population	Results	Conclusion	Quality Score
Beri et al (2009) Michigan	Case-control	93 cases (29 women) and 279 sex- and age-matched controls Exposure defined as statin use in the 12 months preceding tendon rupture	**No difference between cases and controls in the rate of statin use** (OR, 1.10: 95% CI. 0.57-2.13) after adjusting for diabetes, renal disease.rheumatological disease and steroid use	*No association* between statin use and tendon rupture for total population	69%
Savvidou et al (2012) Kentucky	Retrospective observational study	104 patients (98% male; mean age, 47 years; age range, 22-78 years) treated for distal biceps tendon rupture between 2004 and 2010	**No significant association between odds for spontaneous distal biceps tendon rupture and taking statin** (OR, 1.81; 95% CI, 0.56-5.84; *P*=0.32). When adjusted for age: OR, 0.95; *P* = 0.94	Authors concluded a *trend* of association between spontaneous distal biceps tendon rupture and statin therapy	42%
Contractor et al (2015) Private Insurance Database	Retrospective cohort study	34,749 people commencing statins after the beginning of the study period, and 69 498 age- and sex-matched adults not exposed to statins (47.7% female; mean age, 47.6 years, age range, 30-64 years)	Rate of tendon rupture Statin group (n = 334): 5.6 per 1000 patient-years Control group (n = 800): 4.7 per 1000 patient-years **No difference in tendon rupture** between users and non-users of statins after adjusting for comorbidity index, age and sex: IRR, 1.13 (95% CI, 0.98 1.29)	*No association* between statin use and tendon rupture when all statins examined	75%
Lin et al (2015) Taiwan	Prospective cohort study of hyperlipidemia patients followed for 11 years	25,621 patients diagnosed with hyperlipidaemia (52.4% female; mean ± SD age, 57.6 ± 12 years; age range, 30 to ≥ 70 years)	Rotator cuff disease present in 2475 patients (9.7%) with hyperlipidaemia. In patients with hyperlipidaemia, **statin use was associated with a lower risk** of developing rotator cuff disease when compared with no statin use:	Statin use might provide *protection against* rotator cuff disease in patients with hyperlipidaemia, independent of age, sex and diabetes status	83%

Bradford Hill Criteria

- Evidence of causation for temporal relationship, strength of association, reversibility and analogy
- Poor evidence for plausibility, consistency, coherence. No evidence for specificity/dose
- Weak evidence for cause-effect relationship

Overall Conclusion: Tendon rupture during statin therapy is an infrequent occurrence, and one high-quality study demonstrated that event rates were no different from the background rate in the general population. There is insufficient evidence to implicate statin therapy as an established risk factor or causal mechanism for tendon rupture in the general population.

Effects of Statin Treatment on the Development of Tendinopathy: A Nationwide Population-Based Cohort Study (Korea)

Objective: Investigate an association between statin treatment and the development of tendinopathy.

Study design: Cohort study

Methods: 84,102 statin users and 168,204 non-users (controls) followed from 2002-2015. Types of tendinopathy: trigger finger, radial styloid tenosynovitis, elbow epicondylitis, rotator cuff tendinopathy, Achilles tendinitis.

Exclusion criteria: <20 years age in 2002, prescribed a statin in 2002, diagnosed with rheumatoid arthritis, missing/incomplete info

Mean age (years): statin user 49.78 ± 12.89 and nonuser 50.14 ± 14.11

Demographic: Male statin users: 54.39%, male nonusers 56.24%

Primary Outcome: Development of tendinopathy

Definition: Statin user - patient who used statins ≥ cumulative defined daily dose (based on WHO definition)

Hypothesis: Statin use would be associated with an increased risk of tendinopathy development

Table 3. Risk of Tendinopathy Development According to the Statin Treatment. Adapted from Kwak et. al

Tendinopathy	Events, n	HR (95% CI)	P
All Types of Tendinopathy			
Statin Nonuser	63,339	Reference	
Statin user	19,287	1.435 (1.411-1.460)	<.0001

*Consistent results were identified for all included tendinopathy types listed above.

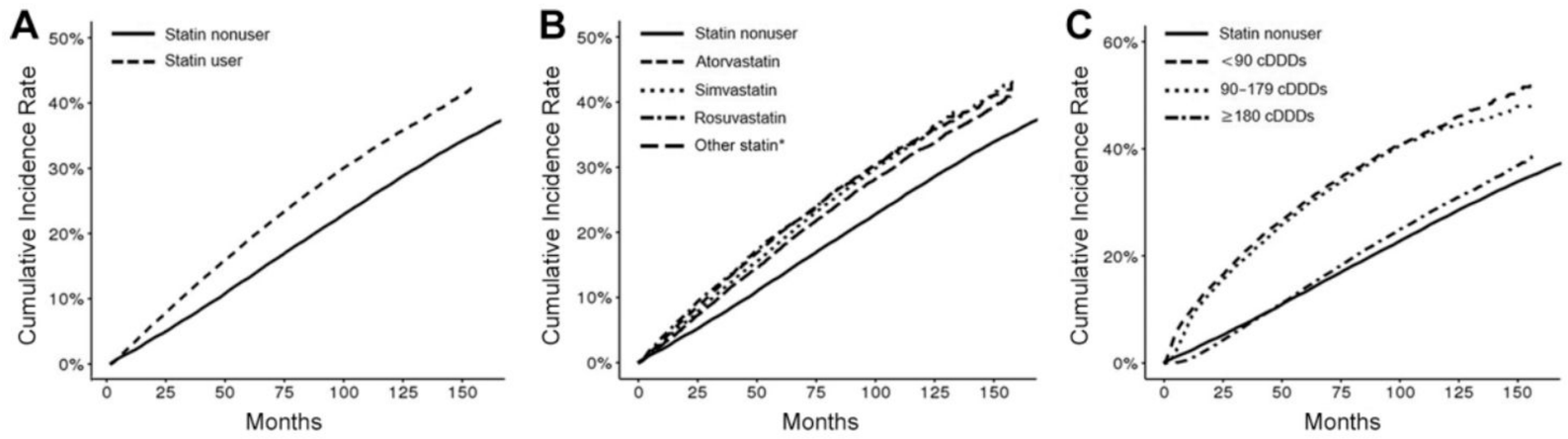

Figure 3. Kwak et al Nationwide Cohort study: Cumulative incidence of the tendinopathy in matched cohort patients (statin users vs nonusers). (A) Overall, (B) by statin type, and (C) by cumulative doses of statin. Pitavastatin, pravastatin, lovastatin, or fluvastatin. cDDD, cumulative defined daily dose.

Overall Conclusion:

Statin use increases incidence of tendinopathy regardless of type of statin and regardless of cumulative dosage

Limitations

Teichtahl et al

- No randomized control trials identified and only 4 studies
- Studies with varied methodology (three examining tendon rupture as primary outcome and one looking at rotator cuff disease)

Kwak et al

- Not a randomized control trial
- Study limited due to only including common types of tendinopathy – Knee tendinopathies were excluded
- Tendon rupture was excluded (due to trauma as a cause)
- Confounding factors not controlled: Smoking, BMI, alcohol
  - Study did control for comorbidities include (Diabetes, Dyslipidemia, CKD) and medications (Steroids and fluoroquinolones)
- Uses a database of racially homogenous cohort in Korea

Neither study measured patient satisfaction or quality of life

Bottom Line

While statins can lead to musculoskeletal issues, they are effective in preventing serious health problems like heart attacks and strokes. Given the balance of risks and benefits, patients should continue taking statins. Primary care physicians should monitor patients closely and discuss these potential side effects to effectively manage and reduce side effects.