CLINICAL IMAGE

Rare and Recurrent Tendon Ruptures in the Context of Long-term Statin Therapy

Sarah Carpinelli, DO, PGY1[1]; John Ashurst, DO[2]; Carlton Richie III, DO[2]

[1] Abrazo Health Family Medicine Residency, Phoenix, AZ
[2] Midwestern University Arizona College of Osteopathic Medicine, Glendale, AZ

CASE REPORT

Statins are the drug of choice to help lower cholesterol levels. Adverse effects, although infrequent, are usually linked to dose increases and improve with medication reduction/cessation. The growing population of patients prescribed statin medications and the nature of their use for lifetime cardiovascular disease (CVD) risk reduction have supported interest in studies focused on the long-term impacts of prolonged statin therapy. While the mechanism is not fully understood, statins have been linked to fibrous changes that contribute to tendinopathy and rupture.

An 86-year-old male presented with successive ruptures of his semitendinosus and latissimus dorsi, two rare tendinous injuries. He maintained an active lifestyle, engaging in regular aerobic exercise and supplemental machine weightlifting, before this unexpected occurrence while moving boxes in his home. His medications included long-term pravastatin (80 mg) and warfarin (2 mg), without history of recent changes.

A review of published literature reveals growing support of the causative relationship of long-term statin treatment and the occurrence of rare tendon ruptures. Clinical indication for medication changes also appears to be supported due to the possibility of patient benefit. Although limited to one patient, this case study provides a unique educational opportunity to update information on a common medication as well as supports further research into the prevalence of this adverse effect and its link to statin therapy that may impact recommended best practices.

CORRESPONDENCE:
Sarah Carpinelli, DO, PGY1| sarah.carpinelli@midwestern.edu
 Print 1877-573X doi: 10.33181/17106

The authors have no conflicts of interest or financial disclosures.

HISTORY

An 86-year-old male presented to the clinic with a chief complaint of pain, swelling, and bruising behind his left knee that had occurred suddenly 1 week prior while moving boxes in his home. The exertion involved was within the patient's normal physical behavior as he maintained an active lifestyle, engaging in regular aerobic exercise and supplemental machine weightlifting. He reported no history of injury or surgery to the extremity. His past medical history included hyperlipidemia and atrial fibrillation, for which he regularly took pravastatin (80 mg) for 20 years and warfarin (2 mg) for 15 years, without a history of recent changes. His cholesterol levels were checked annually and remained well maintained with medication and lifestyle modifications.

Upon initial assessment, the patient's vitals were the following: blood pressure 120/76 mmHg, heart rate 80 bpm, and respiratory rate 12 breaths per minute. His physical exam revealed edema, ecchymosis, and a palpable defect of the posterior left thigh just superior to and along the medial edge of the popliteal fossa (Figure 1). He demonstrated reduced active/passive range of motion (ROM) with left knee flexion/extension as well as reduced strength in left knee flexion. Palpation of the knee joint localized an exaggerated tender point at the point of insertion of the left semitendinosus near the pes anserinus. A diagnosis of left semitendinosus tendon rupture was made clinically, and the patient was returned home on supportive care.

Six weeks later, the patient returned with another spontaneous injury, causing weakness, swelling, and ecchymosis in his left upper extremity (Figures 2 and 3). He had been moving boxes when he felt a "pop" and pain in his axillary region. A tender point was assessed near the humeral insertion point of the left latissimus dorsi muscle. He demonstrated weakness in shoulder adduction and extension. A clinical diagnosis of a tendon rupture to his latissimus dorsi was made.

FIGURE 1

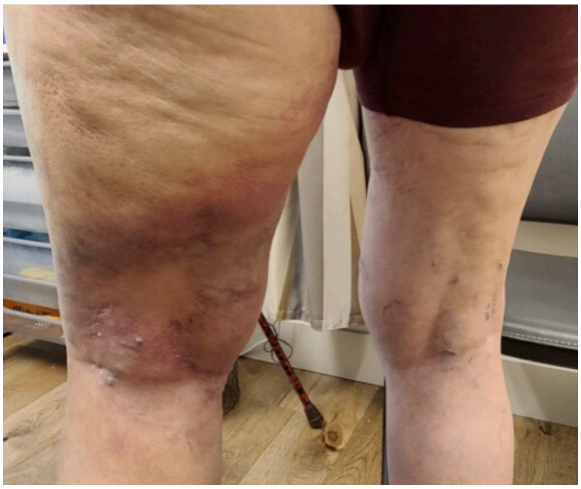


FIGURE 2

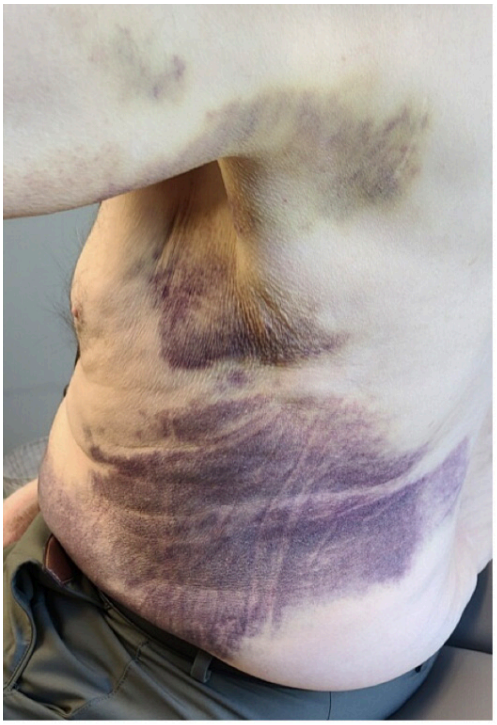
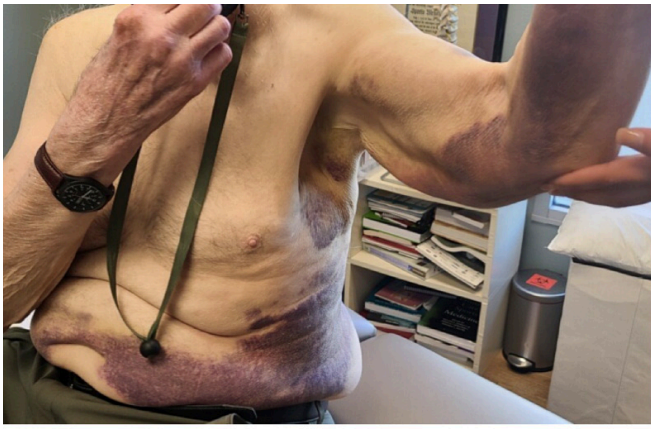


FIGURE 3



QUESTIONS

1. Which of the following are considered reliable ways to diagnose a tendon rupture?

a. Magnetic resonance imaging (MRI)

b. Clinical evaluation

c. Ultrasound

d. All of the above

Correct Answer:
d. All of the above

Special testing, active and passive exams, and assessment of palpable tissue defects have shown high sensitivity and specificity when it comes to diagnosing the occurrence of a tendon rupture and offer important information required before even considering imaging. While studies that have quantified these statistics tend to be isolated to select regions of the body, e.g., the Achilles and biceps tendons, due to the efficacy and accessibility, it is widely accepted that clinical diagnosis of tendon rupture is sufficient.[1,2] The physical exam findings for a latissimus dorsi rupture were well described by George M, et al. in the Journal of the American Academy of Orthopaedic Surgeons, and further demonstrate how a diagnosis can be made in a clinical setting, especially in the case of a complete tear.[3] Similar studies have quantified a higher level of specificity achieved through ultrasound imaging, although the sensitivity remains equivalent. MRI has been shown to provide more detailed information regarding soft tissue injuries; however, due to the high cost and other barriers to access, it is rarely used as a test to confirm tendon rupture.[1]

2. Which of the following is the most common side effect of statin therapy?

a. Hepatic dysfunction

b. Myalgia

c. endinopathy

d. Renal dysfunction

Correct Answer:

b. Myalgia

Statins have been shown to have only low rates of adverse effects, assessing these effects through randomized trials and controlling to a placebo. The most commonly reported adverse reaction was myalgia, while a few experienced more severe effects including tendinopathy, hepatic dysfunction, and renal dysfunction. Reports, however, are more common in clinical practice than data would predict, possibly due to patient awareness of side effects or the effects of comorbidities that are frequently excluded from more controlled studies.[4]

3. When are myalgia adverse effects of statins expected to present themselves with respect to therapy initiation or dose increase?

a. Within 24 hours (dependent upon half-life of the specific statin)

b. Within 1 week

c. Within 1 month

d. Within 6 months

Correct Answer:

c. Within 1 month

On average, studies have shown that myalgia symptoms present 1 month after statin therapy initiation or an increase in dose. Strengthening this temporal relationship, it was found that these symptoms improved 2 weeks after discontinuing the medication. The reoccurrence of these symptoms upon statin drug rechallenge was also found to be 2 weeks. Due to the strong evidence surrounding short-term statin adverse reactions, the timing of symptom onset is a factor currently accepted as one that can strengthen or reduce the likelihood of a pathology's association with the medication.[4]

DISCUSSION

Statins are the drug of choice to help lower cholesterol levels in patients with hyperlipidemia, with the goal of lowering risk of atherosclerotic cardiovascular disease (ASCVD) development and the associated morbidity and mortality. In 2018, statins were prescribed to 92 million patients, with this number growing significantly in recent years.[5] Statins act through inhibition of HMG-CoA (3-hydroxy-3-methylglutaryl–coenzyme A) reductase (HMGR), an enzyme required for the biosynthesis of cholesterol.[6] Reducing levels of intrahepatic cholesterol synthesis also leads to an increase in low-density lipoprotein (LDL) receptor turnover, supporting the removal of this "bad cholesterol" from the bloodstream.[7]

The popularity of this medication is assuredly due to its infrequent association with side effects, as well as its impact on patient ASCVD risk reduction. On average, if adverse effects do occur, it is usually within the first month of treatment or within 1 month of a dose increase, and they typically improve with medication reduction or cessation. As use of statin medications has increased over the last 2 decades, the clinical occurrence of tendon rupture in those undergoing statin therapy has brought the possibility of a causal relationship to the attention of the scientific community. While the mechanism of action is not fully understood, studies have shown disruption of tendon matrices in vitro as well as increased release of matrix metalloproteinase (MMP)-1 and MMP-13 in the context of statin exposure.[8] These fibrous changes are believed to contribute to tendinopathy and an increased risk of tendon rupture.

Tendon ruptures are relatively uncommon injuries and are rarer still in larger tendon structures. Most commonly they are seen in individuals who suddenly and significantly increase their activity level. Larger tendon ruptures, if they occur, are usually seen in professional athletes following escalation of already intense training routines. Chronic conditions such as diabetes, hyperparathyroidism, and poor conditioning can contribute to a patient's increased risk of tendon rupture. Medications such as fluoroquinolone antibiotics and corticosteroid injections have strong causal relationships with tendon ruptures. As this is a well-known risk, it is routinely considered in the medical decision-making process.

A review of published literature finds an expanding collection of studies supporting a strong connection between statin therapy and tendinopathy. In addition to a plethora of clinical cases demonstrating this correlation,[9-14] a nationwide population-based cohort study looking at over 590,000 participants demonstrated a greater risk of tendinopathy in statin users when compared to nonusers.[15] A smaller retrospective study investigating 104 patients with ages ranging from 22 to 78 years also demonstrated that there was a two-times greater risk of distal biceps tendon rupture in those undergoing statin therapy.[16] While some speak to the connection between the two, another cross-sectional study using ultrasound imaging to support contrasting claims of no correlation concluded that there was no evidence of negative impact of statin therapy on the Achilles tendon structure.[17] One review even proposed that a period of missed statin therapy may contribute as a risk factor to increase the chance of a patient experiencing a re-tear of their rotator cuff—although statin influence on rotator cuff injuries has generally contrasted all other tendinopathy trends and has seemed to delineate a separate area of study.[18]

Statins play an important role in reducing CVD in patients with hyperlipidemia, and patient treatment must balance considerations of risks and benefits. While connections to tendon rupture appear significant, some studies have shown discontinuation of statin therapy to return risk levels to baseline.[9,14] In patients who maintain an elevated ASCVD risk score, a change to medications that function through separate mechanisms may reduce the risk of tendon injury in those shown to experience this adverse effect from statin therapy. Alirocumab and evolocumab are monoclonal antibodies that bind and inhibit proprotein convertase subtilisin/kexin type 9 (PCSK9), an enzyme that degrades hepatic LDL receptors, ultimately elevating levels of plasma LDL-C. A comparative study addressing the efficacy and safety of PCSK9 inhibitors actually found them to be the

most effective lipid-lowering agent while also avoiding common statin-related side effects.[19] Additional testing, including measurement of apolipoprotein (B) (Apo(B)) and lipoprotein(a) (Lp(a)) levels, has been shown to provide a more complete assessment of a patient's total ASCVD risk. Clinical consideration of these components can help physicians better assess patient risks and guide pharmacologic de-escalation, limiting unnecessary exposure to potential harm from medications.[20-24]

CONCLUSION

It is important to consider all the risks and benefits of treatment before prescribing any new medications to a patient. When statins are prescribed, it is expected that adverse reactions (most commonly myalgias) will typically present within the first month of either medication initiation or a dosage increase. However, as the prevalence of statin therapy surges in the population, the likelihood of clinically encountering a serious adverse event will rise in conjunction. Studies have shown that long-term statin exposure may have a disruptive effect on tendon matrices. This puts forth a possible explanation underlying the mechanism of injury behind the tendon ruptures that have been noted as an infrequent but severe side effect. It is important to appreciate this connection in the context of the growing population being treated with statins as well as the prolonged therapeutic timelines. In the setting of tendinopathy and rupture, physicians are reminded of the importance of a thorough assessment and including statin adverse effect in the differential, even outside of the context of a recent dose adjustment.

Awareness of this adverse outcome can encourage physicians to include this differential etiology in clinical encounters with unusual tendinopathy and adjust their plan accordingly. Steps must be taken to ensure that injury does not lead to a lasting impact on activity and quality of life. In younger patients who experience tendinopathy in the setting of statin therapy who also maintain an elevated ASCVD risk score, switching to a medication with a different mechanism of action (such as a PCSK9 inhibitor) will allow for continued primary prevention while reducing the risk of further tendon injury. For patients >75 years old, guidelines are less clear as there is no definitive evidence that statin therapy can prevent future coronary artery disease (CAD) or death.[25,26] However, the risk of patient harm with statins has been clearly demonstrated. This balance of risk vs benefit in this population is important to consider in the shared decision-making process and may be aided by further workup through assessment of Apo(B) and Lp(a), helping to guide possible pharmacologic de-escalation.

REFERENCES

1. Amendola F, Barbasse L, Carbonaro R, et al. The acute Achilles tendon rupture: an evidence-based approach from the diagnosis to the treatment. *Medicina*. 2022;58(9):1195. doi: 10.3390/medicina58091195
2. Zwerus EL, van Deurzen DFP, van den Bekerom MPJ, The B, Eygendaal D. Distal biceps tendon ruptures: diagnostic strategy through physical examination. *Am J Sports Med*. 2022;50(14):3956–3962. doi: 10.1177/03635465221129874
3. George MS, Khazzam M. Latissimus dorsi tendon rupture. *J Am Acad Orthop Surg*. 2019;27(4):113–118. doi: 10.5435/JAAOS-D-17-00581
4. Newman CB, Preiss D, Tobert JA, et al. Statin safety and associated adverse events: a scientific statement from the American Heart Association. *Arterioscler Thromb Vasc Biol*. 2019;39(2):e38–e81. doi: 10.1161/ATV.0000000000000073
5. Matyori A, Brown CP, Ali A, Sherbeny F. Statins utilization trends and expenditures in the U.S. before and after the implementation of the 2013 ACC/AHA guidelines. *Saudi Pharm J*. 2023;31(6):795–800. doi: 10.1016/j.jsps.2023.04.002
6. Istvan ES, Deisenhofer J. Structural mechanism for statin inhibition of HMG-CoA reductase. *Science*. 2001;292(5519):1160–1164. doi: 10.1126/science.1059344
7. Ness GC, Zhao Z, Lopez D. Inhibitors of cholesterol biosynthesis increase hepatic low-density lipoprotein receptor protein degradation. *Arch Biochem Biophys*. 1996;325(2):242–248. doi: 10.1006/abbi.1996.0030
8. Eliasson P, Dietrich-Zagonel F, Lundin AC, Aspenberg P, Wolk A, Michaëlsson K. Statin treatment increases the clinical risk of tendinopathy through matrix metalloproteinase release—a cohort study design combined with an experimental study. *Sci Rep*. 2019;9(1):17958. doi: 10.1038/s41598-019-53238-7
9. Moniri NH, Momary KM, McMahon T, Nayee E. Statin-associated Achilles tendon rupture and reproducible bilateral tendinopathy on repeated exposure. *Mayo Clin Proc*. 2018;93(10):1531–1532. doi: 10.1016/j.mayocp.2018.08.005
10. Carmont MR, Highland AM, Blundell CM, Davies MB. Simultaneous bilateral Achilles tendon ruptures associated with statin medication despite regular rock climbing exercise. *Phys Ther Sport*. 2009;10(4):150–152. doi: 10.1016/j.ptsp.2009.01.003
11. Kearns MC, Singh VK. Bilateral patellar tendon rupture associated with statin use. *J Surg Case Rep*. 2016;2016(5):rjw072. doi: 10.1093/jscr/rjw072
12. 12. Pullatt RC, Gadarla MR, Karas RH, Alsheikh-Ali AA, Thompson PD. Tendon rupture associated with simvastatin/ezetimibe therapy. *Am J Cardiol*. 2007;100(1):152–153. doi: 10.1016/j.amjcard.2007.02.068
13. Bove A, Orabona N, De Matteo V, et al. Spontaneous bilateral quadriceps tendon rupture treated with polyethylene terephthalate tape augmentation: report of two consecutive cases. *Jt Dis Relat Surg*. 2022;33(3):666–672. doi: 10.52312/jdrs.2022.764
14. Gowdar SD, Thompson PD. Multiple tendon ruptures associated with statin therapy. *J Clin Lipidol*. 2020;14(2):189–191. doi: 10.1016/j.jacl.2019.12.001
15. Kwak D, Moon SJ, Park JW, Lee DH, Lee JI. Effects of statin treatment on the development of tendinopathy: a nationwide population-based cohort study. *Orthop J Sports Med*. 2023;11(7):23259671231167851. doi: 10.1177/23259671231167851
16. Savvidou C, Moreno R. Spontaneous distal biceps tendon ruptures: are they related to statin administration? *Hand Surg*. 2012;17(2):167–171. doi: 10.1142/S0218810412500153

17. de Sá A, Hart DA, Khan K, Scott A. Achilles tendon structure is negatively correlated with body mass index, but not influenced by statin use: a cross-sectional study using ultrasound tissue characterization. *PLoS One*. 2018;13(6):e0199645. doi: 10.1371/journal.pone.0199645

18. Lee S, Lee N, Shin SJ. Relationship of missed statin therapy and 10-year atherosclerotic cardiovascular disease risk score to retear rate after arthroscopic rotator cuff repair. *Am J Sports Med*. 2023;51(8):1988–1996. doi: 10.1177/03635465231175476

19. Zhao Z, Du S, Shen S, et al. Comparative efficacy and safety of lipid-lowering agents in patients with hypercholesterolemia: a frequentist network meta-analysis. *Medicine (Baltimore)*. 2019;98(6):e14400. doi: 10.1097/MD.0000000000014400

20. Kim K, Ginsberg HN, Choi SH. New, novel lipid-lowering agents for reducing cardiovascular risk: beyond statins. *Diabetes Metab J*. 2022;46(4):517–532. doi: 10.4093/dmj.2022.0198

21. O'Donoghue ML, Rosenson RS, Gencer B, et al. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. *N Engl J Med*. 2022;387(20):1855–1864. doi: 10.1056/NEJMoa2211023

22. Rhainds D, Brodeur MR, Tardif JC. Lipoprotein(a): when to measure and how to treat? *Curr Atheroscler Rep*. 2021;23(9):51. doi: 10.1007/s11883-021-00951-2

23. Jang AY, Lim S, Jo SH, Han SH, Koh KK. New trends in dyslipidemia treatment. *Circ J*. 2021;85(6):759–768. doi: 10.1253/circj.CJ-20-1037

24. Ahmad M, Sniderman AD, Hegele RA. Apolipoprotein B in cardiovascular risk assessment. CMAJ. 2023;195(33):E1124. doi:10.1503/cmaj.230048.

25. Nanna MG, Abdullah A, Mortensen MB, Navar AM. Primary prevention statin therapy in older adults. *Curr Opin Cardiol*. 2023;38(1):11–20. doi: 10.1097/HCO.0000000000001003

26. Lazris A, Roth AR. Overuse of statins in older adults. *Am Fam Physician*. 2019;100(12):742–743.