Statins and tendinopathy: a systematic review

Abstract

Objectives: To systematically review the evidence on whether statin therapy, commonly used in clinical practice to treat hypercholesterolaemia for primary and secondary prevention of cardiovascular disease, contributes to tendinopathy; and to examine causality according to the Bradford Hill criteria.

Study design: A systematic review of studies examining the relationship between statin therapy and tendinopathy. Included studies were rated based on their methodological quality. A best evidence synthesis was used to summarise the results, and Bradford Hill criteria were used to assess causation.

Data sources: Ovid MEDLINE, CINAHL Plus, PubMed and Embase databases.

Study selection: We included adult human studies published in the English language between January 1966 and October 2015. Study designs eligible for inclusion were randomised controlled trials and cross-sectional, cohort or case–control studies.

Data synthesis: Four studies (three cohort studies and one case–control study) were included, with a mean methodological quality score of 67%. Three studies were deemed high quality. Tendon rupture was the primary outcome in three studies, and rotator cuff disease in the other. All studies found no positive association between statin therapy and tendon rupture for the total study population. There was evidence that simvastatin reduces the risk of tendinopathy.

Conclusion: To date, there is a paucity of evidence to implicate statin therapy as a well established risk factor or causal mechanism for tendon rupture in the general population. There is strong evidence that simvastatin reduces the risk of tendinopathy.

The prescription of statin medications has increased over the past two decades.[1] In 2006, 157 million prescriptions for statins were issued in the United States, grossing $16 billion.[2] Since clinical release of the first statin, lovastatin, in 1987, considerable time has elapsed for post-marketing surveillance. Overall, statins are considered to have a well documented safety profile, with less than 2% of patients treated with atorvastatin ceasing the medication because of a drug-attributable adverse event.[3] One area of interest in post-marketing surveillance of statins has been the musculoskeletal system,[4,5] with conjecture that statins may contribute to tendinopathy.

Two significant attempts have been made to relate tendinopathy to statin therapy.[6,7] In a retrospective observational case series of 31 French pharmacovigilance centres to determine the rates of tendon rupture or tendonitis among statin users, Marie and colleagues[7] observed an increase in the number of reported tendinous complications, with eight reports from 1990 to 1995, and 56 from 2001 to 2005. However, this may simply reflect higher prescribing rates of statin therapy over time. Hoffman and colleagues reported pooled data for tendon and joint adverse events among patients using statins,[6] but pooling of different structural outcomes makes interpretation problematic. Neither study included a comparator group to determine the rate of tendinopathy occurring among people not using statin therapy.[6,7] Therefore, no conclusion can be made regarding whether the rates of tendinopathy while using statin therapy differed from the background rate of tendinopathy in the general community.

To assess this question, we performed a systematic review and examined the evidence for potential causation using the Bradford Hill criteria.

Methods

This systematic review was conducted according to the 2009 PRISMA statement.[8]

Search strategy and methodological quality

We searched four databases (Ovid MEDLINE, CINAHL Plus, PubMed and Embase) for the period January 1966 to October 2015 using the search terms described in Appendix 1. The search was limited to adult human studies published in the English language. We also searched the reference lists of included studies. To be included in this systematic review, studies had to report a comparison of a tendinopathy outcome between participants exposed to statins and those not exposed to statins. Study designs eligible for inclusion were randomised controlled trials and cross-sectional, cohort or case–control studies (Appendix 2). We excluded case reports and case series from the best evidence synthesis but include these reports in our analysis of the Bradford Hill criteria for causation.

Two independent reviewers (AJT and SREB) screened the identified articles and scored the methodological quality of included articles using the adapted scoring system of Lievense and colleagues[9,10] (Appendix 3). Each methodological quality item was scored as positive (1), negative (0) or unclear (?), with a maximum possible score of 100%. Where the reviewers disagreed and could not achieve a consensus, a third reviewer (FMC) gave a final judgement. "High quality" was defined as achieving a score above the mean of all quality scores. We also used the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) to assess methodological quality of the included studies.[11]

Full-text articles that were excluded are listed in Appendix 4.

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Best evidence synthesis

We used best evidence synthesis to summarise the data (Box 1).[10,11] Studies were ranked according to their design, with cohort studies considered to be a higher level of evidence than case–control and cross-sectional studies. The level of evidence of studies was determined in conjunction with the quality score calculated for each study. For instance, "limited evidence" was concluded if generally consistent findings were demonstrated in a single cohort study, one or two case–control studies or multiple cross-sectional studies. In contrast, "strong evidence" was supported by generally consistent findings in multiple high-quality cohort studies.

Bradford Hill Criteria for causation

We used the Bradford Hill criteria to determine whether there was adequate evidence of a causal relationship between statin use (the risk factor) and tendinopathy (the disease).[12]

Results

We identified four studies for inclusion in this systematic review (Appendix 2).[13-16] These studies were published between 2009 and 2015 (Box 2). Three were cohort studies and one was a case–control study. One study was conducted in Taiwan[13] and all others in the US. In two studies, patients were recruited as cases from hospital databases,[14,15] with the other studies collecting data from insurance databases.[13,16] When people who were not exposed to statins were recruited, they were age- and sex-matched from the same institute as the index case.[14,16] Tendon rupture was the primary outcome in three studies, and rotator cuff disease in the other.[13]

1 Criteria for determining the level of evidence in best evidence synthesis*

Level of evidence	Criteria for inclusion in best evidence synthesis
Strong evidence	Generally consistent findings in: • Multiple high-quality cohort studies
Moderate evidence	Generally consistent findings in: • 1 high-quality cohort study and > 2 high-quality case–control studies • > 3 high-quality case–control studies
Limited evidence	Generally consistent findings in: • Single cohort study • 1 or 2 case–control studies, or • Multiple cross-sectional studies
Conflicting evidence	Inconsistent findings in < 75% of studies
No evidence	No studies could be found

*Adapted from Lievense et al.[9,10] ◆

Definitions of statin exposure and tendinopathy

Definitions of statin exposure varied, including statin use in the 12 months preceding tendon rupture,[14] or commencing therapy between 2003 and 2010 and having at least 1 year of continuous enrolment in a private insurance database.[16] In the Taiwanese study, patients who used statins for at least 28 days were defined as users.[13] In another study, medication histories were assessed at the time of surgical repair of the ruptured biceps tendon.[15] No measure of compliance was recorded in any study.

In two studies, tendon ruptures were identified by code 727.xx in the International Classification of Diseases, 9th revision (ICD-9).[14,16] In the other tendon rupture study, ruptures were identified historically, whereby spontaneous ruptures were defined as occurring during activities of daily living, and provoked ruptures during strenuous activities.[15] Incident cases of rotator cuff disease were identified by ICD-9, clinical modification (CM) diagnosis codes 726.1, 727.61 or 840.4.[13] The anatomical site of rupture varied, with one study focusing solely on the distal biceps tendon,[15] while others pooled results from various anatomical sites.[14,16]

Characteristics of people with tendinopathy

In the largest study, Contractor and colleagues[16] compared 34 749 people who commenced taking statins with 69 498 age- and sex-matched people who did not use statins. Beri and colleagues'[14] case–control study compared 93 patients with tendon rupture with 279 age- and sex-matched controls without tendon rupture. Savvidou and colleagues[15] reviewed a cohort of 104 patients with distal biceps tendon rupture. In the Taiwanese cohort, Lin and colleagues[13] identified 25 621 patients with hyperlipidaemia, with 9.7% of these having rotator cuff disease. Participants' ages ranged from 22 to 78 years. The proportion of women in the study populations ranged from 2% to 52.4%.

Is statin therapy associated with tendinopathy?

No study found an association between statin therapy and tendon rupture for the total population (Box 2).[14-16] Beri et al[14] demonstrated an association between tendon rupture and statin therapy for women only (odds ratio [OR], 3.76; 95% CI, 1.11–12.75; $P = 0.043$). However, only 22 people with tendon ruptures in their study had been exposed to a statin. Subgroup analyses based on sex further reduce the number of people with tendon ruptures exposed to statins and this result should therefore be treated with caution. The study authors repeated their work in an independent and larger cohort and found no predisposition by sex to statin-associated tendinopathy.[16] In this larger study, subgroup analyses found that users of atorvastatin were at higher risk than those not taking statins (incidence rate ratio [IRR], 2.40; $P = 0.0001$), while simvastatin was protective (IRR, 0.77; $P < 0.05$). In the other tendon rupture study included in our review, although the authors concluded there was "a trend of association" between spontaneous distal biceps tendon

2 Epidemiological evidence examining statin use and tendinopathy

Study	Design and setting	Population	Results	Conclusion	Quality score
Beri et al (2009)[14]	Case–control study at Michigan State University (2002–2007)	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 Statin exposure was a significant risk factor for tendon rupture in women (OR, 3.76, 95% CI, 1.11–12.75) but not in men (OR, 0.66; 95% CI, 0.29–1.51)	No association between statin use and tendon rupture for total population Subgroup analysis suggests that women with tendon rupture were more likely to be taking statins	69%
Savvidou et al (2012)[15]	Retrospective observational study at Institute for Hand and Microsurgery, Louisville, Kentucky (2004–2010)	104 patients (98% male; mean age, 47 years; age range, 22–78 years) treated for distal biceps tendon rupture between 2004 and 2010 Spontaneous rupture ($n = 19$) defined as occurring during activities of daily living Provoked rupture ($n = 85$) defined as occurring during strenuous activities	Of the 104 patients, 19 were taking statins (5 in spontaneous rupture and 14 in provoked rupture group) 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)[16]	Retrospective cohort study using private insurance database	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) The most commonly prescribed drug was simvastatin (57.4%; 19 902) followed by atorvastatin (19.0%; 6596), lovastatin (16.5%; 5736) and pravastatin (5.2%; 1794), with others accounting for less than 2%. When assessing the risk with individual statins, atorvastatin users had a significant risk of tendon rupture compared with controls (IRR, 2.40; $P = 0.0001$). Conversely, simvastatin use was associated with a lower risk of rupture (IRR, 0.77; $P < 0.05$)	No association between statin use and tendon rupture when all statins examined	75%
Lin et al (2015)[13]	Prospective Taiwanese cohort study of patients diagnosed with hyperlipidaemia in 2000 and followed for 11 years (with or without statin use), from the National Health Insurance Research Database	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: • Rosuvastatin: HR, 0.41; 95% CI, 0.35–0.49; $P < 0.0001$) • Simvastatin: HR, 0.62; 95% CI, 0.54–0.71; $P < 0.0001$ • Other pooled statins (lovastatin, fluvastatin, pravastatin): HR, 0.66; 95% CI, 0.60–0.72; $P < 0.0001$)	Statin use might provide protection against rotator cuff disease in patients with hyperlipidaemia, independent of age, sex and diabetes status	83%

OR = odds ratio. IRR = incidence rate ratio. HR = hazard ratio. ◆

ruptures and statin therapy (OR, 1.81; 95% CI, 0.56–5.84; $P = 0.32$), the direction of the result was changed when multivariate analyses adjusted for age (OR, 0.95; $P = 0.94$).[15]

In the study examining rotator cuff disease, exposure to simvastatin (hazard ratio [HR], 0.62; 95% CI, 0.54–0.71; $P < 0.001$), rosuvastatin (HR, 0.41; 95% CI, 0.35–0.49; $P < 0.001$) or other pooled statins (HR, 0.66; 95% CI, 0.60–0.72; $P < 0.001$) was associated with a reduced risk of rotator cuff disease.[13]

What does best evidence synthesis show regarding the association between statin therapy and tendinopathy?

The mean methodological score was 67%, with scores ranging from 42% to 83% (Appendix 5). Three of four studies were considered to be of high quality.[13,14,16] The RoBANS found low risk of bias on most criteria in the studies (Box 3). Overall, the best evidence synthesis indicated limited evidence to conclude there was no association between statin therapy and tendon rupture. There was strong evidence that simvastatin was associated with a reduced risk of tendon rupture or rotator cuff disease.

What evidence is there for causation according to the Bradford Hill criteria?

We found that there was, at best, evidence for causation with respect to four of the Bradford Hill criteria: temporal relationship, strength of the association, reversibility and analogy (Box 4). There was poor evidence for the remaining criteria (plausibility, consistency and coherence) and no available evidence for specificity or a dose–response relationship. Overall, there was, at best, weak evidence for a cause–effect relationship. Nevertheless, the paucity of data in this field makes adequate interpretation of the Bradford Hill criteria difficult.

Discussion

In this review, we identified four studies examining the role of statin therapy in tendinopathy. Best evidence synthesis showed strong evidence that simvastatin reduced the risk of tendon rupture and rotator cuff disease, and limited evidence to conclude any adverse association between statin therapy and tendon rupture. Our findings suggest it is unlikely that statin therapy was a causative mechanism for tendon rupture among the total population of statin consumers.

The rate of tendon rupture among statin users was similar to the background rate in the general population.[16] Contractor et al[16] found that among just under 35 000 people who had commenced statin therapy, the rate of tendon rupture was small ($n = 334$) and no different from the rate ($n = 800$) observed in nearly 70 000 sex- and age-matched people not exposed to a statin. Indeed, in this large study, simvastatin users had a reduced risk of tendon rupture,[16] a finding corroborated by another study demonstrating that statin exposure reduced the risk for rotator cuff disease.[13]

In 2003, 3.2 million people in France received statins, with only 13 statin-attributed tendon disorders reported in the national network of pharmacovigilance centres.[7] As well as occurring infrequently, no study has reported an increased risk of tendinopathy related to statin therapy when analysing the total populations.[14,16] While one study found an increased risk of tendon rupture in women,[14] caution must be exercised when interpreting this subgroup analysis as the number of tendon ruptures for the total population was low.

It may be that case reports of tendon rupture among statin users gained notoriety because of the extreme nature of ruptures (eg, bilateral tendon ruptures) (Box 5).[21-25] However, many of these reports are complicated by other risk factors for tendinopathy, such as

3 Risk of Bias Assessment Tool for Nonrandomized Studies[11]

Bias type	Description	Risk of bias			
		Beri et al (2009)[14]	Savvidou et al (2012)[15]	Contractor et al (2015)[16]	Lin et al (2015)[13]
Selection of participants	Selection bias caused by inadequate selection of participants	Low	Low	Low	Low
Confounding variables	Selection bias caused by inadequate confirmation and consideration of confounding variable	Low	High	Low	Low
Measurement of exposure	Performance bias caused by inadequate measurement of exposure	Low	Low	Low	Low
Blinding of outcome assessment	Performance bias caused by inadequate blinding of outcome assessment	Unclear	Unclear	Unclear	Unclear
Incomplete outcome data	Attrition bias caused by inadequate handling of incomplete outcome data	Low	Unclear	Low	Low
Selective outcome reporting	Reporting bias caused by selective reporting of outcomes	Low	Low	Low	Low

4 Evidence for a causal relationship between statin therapy and tendinopathy, according to the Bradford Hill criteria

Bradford Hill criterion and description	Evidence supporting or refuting a causal relationship between statin use and tendinopathy
Temporal relationship This is an essential criterion. For a possible risk factor to be the cause of a disease, it must come before the disease. This is generally easier to establish from cohort studies than from cross-sectional or case–control studies, when measurements of the possible cause and the effect are made at the same time	Contractor et al (2015)[16] • 34 749 people commenced taking statins after the beginning of the study period • No differences in tendon rupture between users and non-users of statins after adjusting for comorbidity index, age and sex for total population • Subgroup analyses: while atorvastatin use significantly increased the risk for rupture, simvastatin use was associated with a significant risk reduction Lin et al (2015)[13] • All statins were associated with reduced risk for rotator cuff disease among people with hyperlipidaemia, independent of age, sex and diabetes mellitus Therefore, there is no supportive evidence to fulfil a temporal relationship, other than in one subgroup analysis for atorvastatin use. Indeed, temporal relationship suggests a reduced risk of tendon rupture and rotator cuff disease in simvastatin users
Plausibility A risk factor associated with a disease is more likely to be the cause of the disease if the association found is consistent with knowledge obtained from other sources, such as animal experiments and experiments on biological mechanisms. However, this criterion must be used with care as a lack of plausibility may simply reflect a lack of scientific knowledge	de Oliveira et al (2013)[17] • Evidence of degradation and remodelling processes in the extracellular matrix of the Achilles tendon of rats treated with statins Ferreira et al (2014)[18] • Simvastatin and rosuvastatin were associated with reduced lung inflammation in mice[18]
Consistency If similar results have been found in different populations using different study designs, the association is more likely to be causal as it is unlikely that all studies were subject to the same types of errors (chance, bias or confounding). However, a lack of consistency does not exclude a causal association, as different exposure levels and other conditions may reduce the impact of the causal factor in certain studies	Contractor et al (2015)[16] • Atorvastatin was associated with an increased risk of tendon rupture Marie et al (2008)[7] • Tendon complications were most commonly seen with atorvastatin (35/96); unclear whether atorvastatin was the most commonly prescribed statin Contractor et al (2015)[16] and Lin et al (2015)[13] • Simvastatin was associated with reduced risk of tendon rupture and rotator cuff disease
Strength of an association The strength of an association is measured by the size of the relative risk. A strong association is more likely than a weak association to be causal, as a weak association could more easily be the result of confounding or bias	Beri et al (2009)[14] • Statin exposure was a significant risk factor for tendon rupture in subgroup analyses only, for women (OR, 3.76; 95% CI, 1.11–12.75) Contractor et al (2015)[16] • Atorvastatin users had a significant risk of tendon rupture compared with controls (IRR, 2.4; $P = 0.0001$) • Simvastatin use was associated with a lower risk of tendon rupture (IRR, 0.77; $P < 0.05$) Lin et al (2015)[13] • Simvastatin associated with reduced risk of rotator cuff disease (HR, 0.62; 95% CI, 0.54–0.71; $P < 0.0001$)
Dose–response relationship Further evidence of a causal relationship is provided if increasing levels of exposure lead to an increasing risk of disease	No available evidence
Specificity If a particular exposure increases the risk of a certain disease but not the risk of other diseases, this is strong evidence in favour of a cause–effect relationship. However, one-to-one relationships between exposure and disease are rare, and lack of specificity should not be used to say that a relationship is causal	No available evidence
Reversibility When the removal of a possible risk factor results in a reduced risk of disease, the likelihood that this association is causal is increased. Ideally, this should be assessed by conducting a randomised intervention trial. For many exposures or diseases, such randomised trials are not possible in practice	Chazerain et al (2001)[19] • Weak evidence only: a case series ($n = 4$) demonstrated that discontinuation of a statin resulted in resolution of tendinopathy in all four patients Marie et al (2008)[7] • Tendon symptoms abated upon cessation of drug, and symptoms recurred in all seven patients in whom statin therapy was reinstituted

(*continued*)

4 Evidence for a causal relationship between statin therapy and tendinopathy, according to the Bradford Hill criteria (Continued)

Bradford Hill criterion and description	Evidence supporting or refuting a causal relationship between statin use and tendinopathy
Coherence The suggested cause–effect relationship should essentially be consistent with the natural history and biology of the disease	Tendinopathy can result from many mechanisms, including sport or heavy physical activity, hyperlipidaemia and medications such as fluoroquinolones
Analogy The causal relationship will be further supported if there are similarities with other (well established) cause–effect relationships	Other drug classes (fluoroquinolones) are a well established causal mechanism for tendinopathy[20]

OR = odds ratio. IRR = incidence rate ratio. HR = hazard ratio. ◆

hypercholesterolaemia,[26,27] diabetes mellitus,[28,29] fluoroquinolone use[20,24] or extreme exertion.[21] Higher serum cholesterol concentrations are associated with a thicker Achilles tendon,[26,27,30,31] with localised oedema and inflammation, interfering with function and possibly contributing to tendon rupture.[32,33] It has been found that after treatment with atorvastatin for 12 months, Achilles tendon thickness regressed among 15 heterozygous patients with familial hyperlipidaemia and tendon xanthoma.[34] It is therefore difficult to distinguish whether tendinopathy was a result of drug intervention or whether it was the pathological process necessitating statin therapy that increased the risk of tendinopathy (ie, confounding by indication). Indeed, as part of the metabolic syndrome, people with dyslipidaemia often have co-existing hyperuricaemia and diabetes mellitus, factors recognised to independently increase the risk of tendinopathy.[13,28,35,36] An Australian study found that, compared with 5159 age- and sex-matched controls without diabetes, there was a greater risk of tendon rupture requiring hospitalisation among people with type 2 diabetes ($n = 1296$).[36] In the limited number of studies we found examining tendinopathy and statin use, three made a concerted effort to adjust for confounders such as diabetes mellitus or hyperuricaemia.[13,14,16] Likewise, two studies found that no patients who had ruptured tendons had been exposed to fluoroquinolones.[14,15] While Contractor et al[16] did not report the number of people exposed to fluoroquinolones, this was a factor in the comorbidity index used in their regression analyses.

Another potential limitation to better understanding the possible association between statin therapy and tendon-related disorders is the heterogeneity among studies. For instance, Beri et al[14] pooled tendon ruptures from multiple anatomical sites. It may be that the risk of tendon rupture is site-specific. Savvidou et al[15] circumvented this limitation by only examining distal biceps tendon rupture, concluding that there was a trend towards increased spontaneous distal biceps tendon ruptures in patients taking statins. However, this trend was not statistically significant, and results changed direction when age was included in the multivariate analyses.

5 Case reports examining statin use and tendinopathy

Study	Patient age, sex	Comorbidities	Statin	Anatomical site	Potential confounding
Carmont et al (2009)[21]	47 years, male	Familial hypercholesterolaemia	Simvastatin, 40 mg/day Exposure duration, 12 weeks	Bilateral Achilles tendon rupture (simultaneous)	Rock-climber who trained at least once per week for past 27 years, with familial hypercholesterolaemia
Rubin et al (2011)[22]	58 years, male	Hypertension	Simvastatin, 80 mg/day Exposure duration, 4 years	Complete bilateral quadriceps tendon rupture (simultaneous)	None identified
Celik et al (2012)[23]	56 years, male	Abdominal aortic aneurysm repair	Rosuvastatin, dose not stated Exposure duration, 4 years	Complete bilateral quadriceps tendon rupture while climbing stairs	None identified
Ganske et al (2012)[24]	58 years, male	Recurrent otitis media treated with levofloxacin, 750 mg/day for 5 days (10 days before event)	Simvastatin, 20 mg/day Exposure duration not stated	Hip tendinopathy	Exposure to fluoroquinolone
Nesselroade et al (2010)[25]	56 years, male	Nil	Atorvastatin, 20 mg/day Exposure duration, 3 years	Bilateral quadriceps tendon rupture (simultaneous)	Football referee

Our systematic review has several limitations. We identified only a small number of studies, and no randomised controlled trials. Studies varied considerably in their methodology, with three studies examining tendon rupture as the primary outcome and only one examining rotator cuff disease. Moreover, different clinical populations (eg, patients in university hospitals, private insurance databases and microsurgery institutes) exposed to various statins, with different follow-up times, as well as variations in handling of potential confounders and tendon rupture outcomes at different anatomical sites, contributed to the heterogeneity of studies. Along with the absence of randomised controlled trials, this precluded a meta-analysis of these data. We have instead used a best evidence synthesis approach,[9,10] in which studies above the mean quality score of all available evidence are deemed high quality. This is a limitation, as even among a collection of generally poor studies, half will be deemed high quality. Although this may influence best evidence synthesis, it is a true reflection of the available published literature and this is the first systematic review of this topic. We also limited our search strategy to studies written in English. However, this is unlikely to have biased our results, as we identified no abstracts in other languages. Moreover, we also used the RoBANS, which found low risk of bias on most criteria.

Conclusions

On the basis of the limited data available, tendon rupture while using statin therapy is an infrequent occurrence, and one high-quality study demonstrated that event rates were no different to the background rate in the general population. Indeed, two high-quality cohort studies provided strong evidence that simvastatin reduces the risk of tendinopathy. There is limited evidence for causality between statin therapy and tendon rupture.

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