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STATINS: BITTER ENEMIES OF TENDONS OR NOT? A SYSTEMATIC REVIEW OF CLINICAL EVIDENCE

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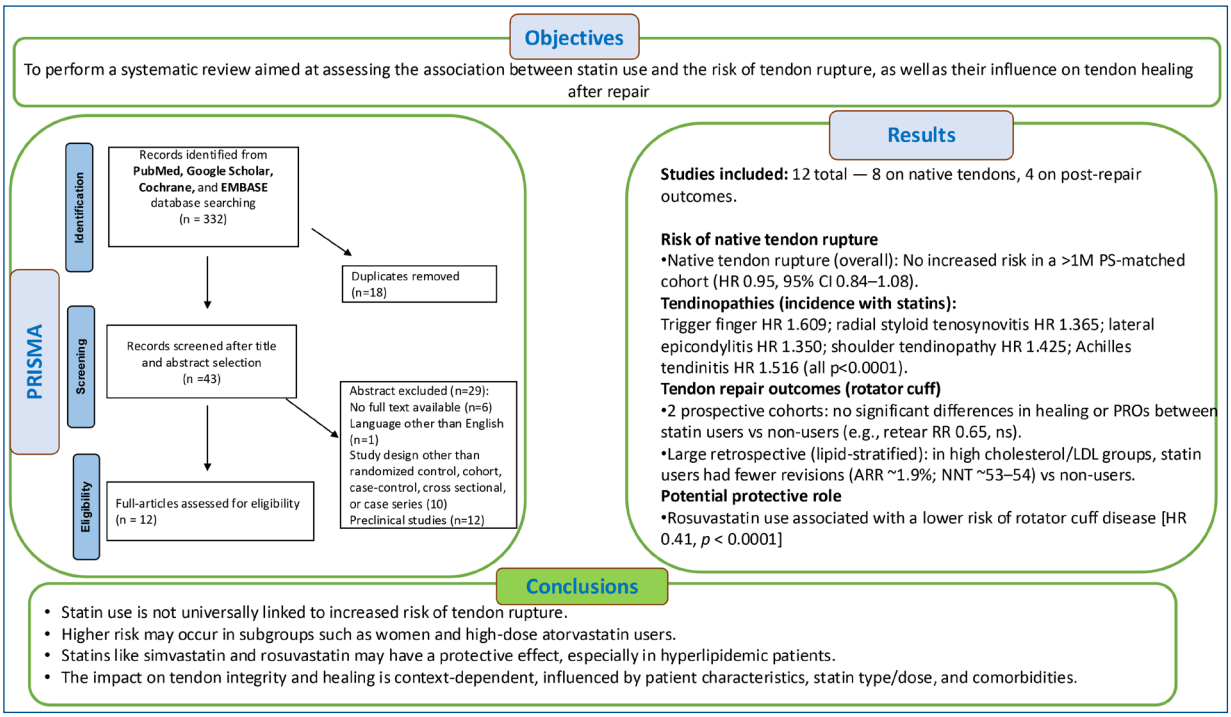
ABSTRACT – *Objective:* Tendon tears cause significant disability, especially in the elderly. Lipid metabolism was shown to play a role in tendon tear pathogenesis. Statins, which lower cholesterol levels, have been associated with tendinopathies and tendon tears as possible adverse events. This systematic review evaluates the association between statin use and tendon rupture risk, as well as statins' influence on tendon healing after repair.

Materials and Methods: A literature search was conducted on PubMed, Embase, and Google Scholar databases using specific search strings related to statins and tendons. The inclusion criteria included randomized controlled trials (RCTs), retrospective or prospective studies on humans, articles written in English, papers published in indexed journals, and articles evaluating the relationship between statins and tendons. The quality of RCTs was assessed through the Cochrane Risk of Bias tool, while the risk of bias for non-randomized studies was evaluated according to the modified ROBINS-I tool.

Results: Twelve studies were included; eight studies investigated statin effects on native tendons, and four evaluated outcomes after tendon repair. Across over 1 million patients, a large cohort study found no significant increase in the risk of native tendon rupture among statin users (HR 0.95, 95% CI 0.84-1.08). Conversely, a retrospective study found that hyperlipidemic patients treated with statins had a significantly higher retear rate after rotator cuff repair compared to the control group (OR 6.5, $p < 0.001$). Furthermore, statin use was associated with an increased risk of tendinopathies, including trigger finger (HR 1.435), radial styloid tenosynovitis (HR 1.365), and Achilles tendinitis (HR 1.516) ($p < 0.0001$ for all). However, protective effects were observed for rotator cuff disease with rosuvastatin (HR 0.41, $p < 0.0001$).

Conclusions: The effect of statins on tendons may be modulated by variables such as sex, tendon type, statin formulation, and comorbidities. Hence, statin therapy does not universally increase tendon rupture risk but may influence tendon integrity and healing in a patient-specific manner. Further high-quality studies are needed to define these relationships better and optimize clinical recommendations.

KEYWORDS: Statins, HMG-CoA-reductase, Tendons, Tendinopathy, Tendon rupture, Statin adverse events, Atorvastatin, Simvastatin.



Graphical Abstract. A schematic summary of the systematic review process and findings.

INTRODUCTION

Tendon tears can lead to significant disability, particularly in elderly patients who may not be suitable candidates for surgery[1]. Several intrinsic and extrinsic factors contribute to the development of tendon tears. In particular, recent evidence showed how lipid metabolism may play a role in tendon tears pathogenesis[2-4]. Clinical studies suggest that hyperlipidemia independently increases the risk of rotator cuff tears, and elevated cholesterol levels have been observed in patients with rotator cuff tears[5,6]. Indeed, lipids accumulate within the extracellular matrix, affecting tendons' mechanical properties, especially in conditions, such as familial hyperlipidemia[7-9]. Moreover, animal studies have suggested that hyperlipidemia impairs tendon-bone healing after tendon repair[10]. Poor tendon-bone healing after surgical repair could be secondary to oxidized low-density lipoprotein deposition, altering the mechanical characteristics of the tendon and leading to persistent inflammation as well as impaired blood circulation[6,11]. Statin drugs (i.e., atorvastatin, simvastatin, rosuvastatin, fluvastatin, lovastatin) work by inhibiting HMG-CoA reductase, which is a rate-limiting step in cholesterol biosynthesis[12,13]. They have been demonstrated to significantly lower low-density lipoprotein cholesterol (LDL-C) levels by 20-50%, exerting their cardiovascular protective effect, but are also able to lower triglyceride levels by 10-20% and perhaps elevate high-density lipoprotein cholesterol (HDL-C) levels by 5-10% in the blood[12,14,15]. Although these drugs are generally well tolerated, possible adverse events were reported, including hepatotoxicity and myotoxicity[16,17]. Moreover, tendinopathies and tendon tears have been recorded with statin use[18,19]. The association between statin use and tendon rupture is biologically plausible since statins reduce cholesterol synthesis, inhibit metalloproteinases, and promote apoptosis, weakening tendon integrity[10,20-22]. Experimental evidence indicates that statins may impact the tendon-to-bone interface by modulating collagen synthesis, inhibiting matrix metalloproteinases (MMPs), and regulating inflammatory mediators like COX-2 and prostaglandins[22]. Additionally, statins affect angiogenesis and nitric oxide bioavailability, two important processes in tendon repair. Depending on the systemic metabolic state and the local environment, these pleiotropic effects may either hinder or facilitate healing[21,23]. Previous studies[17-19] have yielded conflicting results regarding the impact of statins on tendons, likely due to heterogeneity in study design, endpoints, and population profiles. Additionally, although statins are expected to mitigate tendon degeneration by lowering cholesterol levels, paradoxical reports of statin-associated tendinopathies and tendon ruptures have emerged, although this effect

could be due to the altered metabolic state given by hypercholesterolemia itself. Hence, the main outcome of this comprehensive review is to evaluate whether the use of statins is associated with the risk of rupture of both native tendons and repaired tendons. The secondary outcome of the study is to assess whether the use of statins could potentially influence the healing of tendons after surgery.

MATERIALS AND METHODS

This systematic review was conducted in adherence with Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines. The present systematic review protocol was registered on PROSPERO (registration No. CRD42024582023). Screening of the literature was performed on PubMed, Embase and Cochrane databases through the following search terms: "statins" OR "HMG-CoA reductase inhibitors" OR "HMG CoA" "cholesterol lowering drugs" AND "tendons" OR "biceps" OR "rotator cuff" OR "Achilles tendon" OR "patellar tendon" OR "quadriceps tendon". Google Scholar was used as a supplementary source because of its limitations in terms of reproducibility. Studies published from 2000 were included in the present systematic review. Two reviewers independently conducted the screening process (G.A. and M.M.), based on title and abstract review. Inclusion criteria were: (1) randomized clinical studies; non-randomized clinical studies carried on humans; (2) English language; (3) peer-reviewed papers published in indexed journals; and (4) report on clinical outcomes in statin-exposed individuals, either with or without a comparison group: (i) adverse outcomes such as tendon rupture or tendinopathy in native tendons following statin exposure, or (ii) postoperative outcomes following tendon repair (e.g., retear rate, healing quality, or functional scores). Control groups, where present, included individuals not exposed to statins, and in some cases, individuals with hyperlipidemia not treated with statins. Studies that compared different statin types, dosages, or durations of use were also included. Outcomes of interest were tendon rupture (partial or full thickness), clinical diagnoses of tendinopathies (e.g., trigger finger, rotator cuff tendinopathy), and healing outcomes after tendon surgery (e.g., MRI findings, patient-reported outcome scores, revision rates).

Pre-clinical studies, reviews, meta-analyses, and papers written in other languages were excluded from the research.

Following the screening part, the full text of the included articles was downloaded, and the reference list was further evaluated for additional missing studies. Agreement between the two independent reviewers was assessed using Cohen's kappa coefficient, which was 0.81, indicating strong agreement[24]. If discrepancies were encountered, a third senior investigator (B.D.M.) was responsible for consensus. The level of evidence of each study was graded according to the 2011 Oxford Center for Evidence-Based Medicine (OCEBM) recommendations[25].

The quality of RCTs was assessed through the Cochrane Risk of Bias tool for Randomized Controlled Trials[26]. The risk of bias for non-randomized studies was performed according to the modified ROBINS-I tool[27].

RESULTS

The PRISMA flowchart is presented in Figure 1. A total of 12 studies ultimately met the criteria for inclusion in this review. Eight studies evaluated the effects of statins on native tendons (Table I), and four studies assessed the relation between statins and re-rupture after arthroscopic rotator cuff repair (Table II). The included studies comprised two prospective cohort studies, seven retrospective cohort studies, two cross-sectional studies, and one case-control study. The sample sizes of the intervention groups ranged from 33 to 526,351 patients. The outcomes examined included tendon rupture risk, statin exposure, and tendon imaging findings, incidence and development of tendinopathy, and functional scores following rotator cuff repair surgery.

Risk of bias assessment

All the included studies were non-randomized controlled trials. The ROBINS-I tool was used for the assessment. Potential sources of bias were analyzed, such as confounding variables, the way patients were selected, how interventions were categorized, any departures from the planned treatments, gaps in the data, how outcomes were assessed, and which results were ultimately chosen for reporting. Each of them was assigned an evaluation, grading the level of risk[27]. Among the studies assessed, one study showed a low risk of bias, six studies had a moderate risk of bias, and five studies demonstrated a serious risk of bias (Figure 2).

Statins and native tendons

Analyzing 1,052,702 propensity score (PS) matched patients, Spoendlin et al[28] conducted a retrospective cohort study, examining the risk

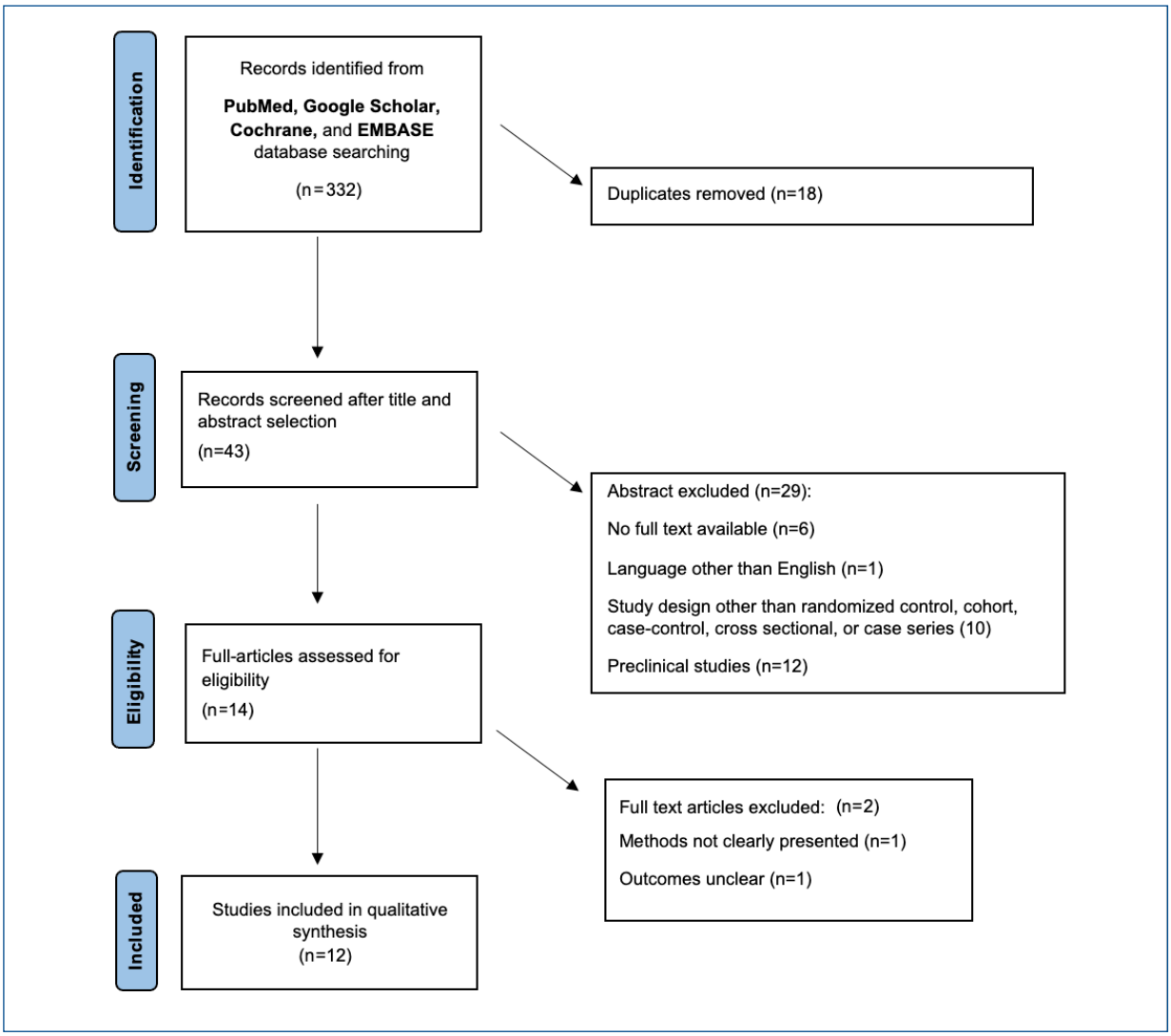


Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flowchart of the systematic literature review.

of Achilles or biceps tendon rupture in statin *vs.* non-statin users, with a mean follow-up of 2.98 years in the treatment group and 3.13 years in the control group, respectively. After multivariate adjustment and PS matching, the hazard ratio of 0.95 (CI 95%, 0.84-1.08) did not reveal a statistically significant difference in tendon rupture risk between patients taking statin medication compared to those not taking statins.

Savvidou et al[29] conducted a cross-sectional study of 104 postoperative patients, including 19 who were taking statins, to evaluate biceps tendon retear rates. They report a non-significant increase in the odds ratio for biceps tendon rupture of 1.81 (CI 95% 0.56 to 5.84, p = .320) in patients taking statins.

The case-control study by Beri et al[30] included 93 cases of tendon rupture and 279 sex and age-matched controls, with exposure being defined as statin use in the 12 months preceding the injury. There was no statistically significant difference observed in statin use between the cases and controls in the study, both in univariate analysis [odds ratio (OR) = 1.0, 95% confidence interval (CI) 0.54-1.84] and in multivariate analyses after adjusting for potential confounding variables (adjusted OR = 1.10, 95% CI 0.57-2.13). In the female subgroup, statin use showed a positive association with tendon rupture, with an OR of 3.09 (95% CI 1.04-9.25, p = .0430, which remained statistically significant after adjusting for diabetes, steroid use, rheumatologic disease, and chronic renal disease (adjusted OR = 3.76, 95% CI 1.11-12.75, p = .03).

In a cross-sectional study involving 66 patients, including 33 statin users, de Sá et al[37] analyzed differences in Achilles tendon imaging between statin users and non-users. They did

Table I. Studies investigating the use of statins and their possible correlation with native tendon ruptures.

Publication	Study design	Level of evidence	Patients' characteristics	Outcome	Follow-up	Main findings
Spoendlin et al[28]	Retrospective cohort	III	Statin users: 526,351 patients (262,099 females, 264,252 males), mean age 65.3y Statin nonusers: 526,351 (264,380 females, 261,971 males), mean age 66.3y	Achilles or biceps tendon rupture	Mean FU in statin users: 2.98 years Mean FU in statin nonusers: 3.13 years	Statin use was not associated with statistically significant increased risk of Achilles or biceps tendon rupture in men irrespective of gender, age, statin dose or treatment duration (CI 0.84-1.08)
Savvidou et al[29]	Cross-sectional	IV	104 patients (102 males, 2 females) surgically treated for distal biceps tendon injuries with a mean age of 47y	Association between statin use and distal biceps rupture	/	Statin administration OR = 1.81 of spontaneous distal biceps tendon rupture (CI 0.56-5.84, $p = 0.32$)
Beri et al[30]	Case-control	III	93 cases of tendon rupture (64 males, 29 females), mean age 49.0y 279 matched controls (192 males, 87 females), mean age 49.0y	Association between statin use and tendon rupture risk	/	No significant difference between cases and controls in the rates of statin use (CI 0.54-1.84, CI 0.5-2.13). Statin use was significantly associated with tendon rupture in females (OR = 3.09, $p = 0.043$)
de Sà et al[37]	Cross-sectional	IV	Statin users (ST): 33 patients (29 males, 4 females), mean age 69y Comparison group (CG): 33 patients (29 males, 4 females), mean age 63y	Ultrasound-based assessment of tendon structure (cross-sectional area, collagen organization)	/	Achilles tendon cross-sectional area (ST 59.7 cm^3, CG 59.9 cm^3) and % echo-type I patterns (ST 70%, CG 74%) were equivalent in the two groups. There was a negative correlation between BMI and longitudinal collagen organization (rs = -0.25, $p = 0.042$)
Contractor et al[31]	Retrospective cohort	III	Statin group: 34,479 patients Sex-matched statin nonusers: 69,498 patients Mean age 47.6y	Incidence of tendon rupture and statin formulation-specific risk	2.4 years	When adjusted for comorbidities (IRR = 1.12, CI 0.98-1.27), age and gender (IRR = 1.12, CI 0.98-1.29), no difference in the risk of tendon rupture among users and nonusers. Atorvastatin had a significant risk of tendon rupture compared with controls (IRR = 2.4, $p < .0001$), while simvastatin was significantly associated with a lower risk of tendon rupture (IRR = 0.77, $p < .05$)

Continued

Table I *(Condinued).* Studies investigating the use of statins and their possible correlation with native tendon ruptures.

Publication	Study design	Level of evidence	Patients' characteristics	Outcome	Follow-up	Main findings
Kwak et al[32]	Retrospective cohort	III	Statin users: 84,102 patients (38,358 females, 45,744 males), mean age 49.78y Statin nonusers: 168,204 patients (73.612 females, 94,592 males), mean age 50.14y	Incidence of multiple tendinopathies among statin users	13 years	Statin users have greater risk of tendinopathy, regardless of statin type: trigger finger, HR = 1.435; radial styloid tenosynovitis, HR = 1,365; elbow epicondylitis, HR = 1.425; shoulder tendinopathy, HR = 1.425; Achilles tendinitis, HR = 1.516; p <.0001 for all
Eliasson et al[33]	Retrospective cohort	III	Statin users: 37,177 patients (19,323 females, mean age 68.4y; 17.854 males, 69.5y Statin never-users: 55,846 patients (32,987 patients, mean age 69.5y; 22,859 patients, mean age 66.6y)	Risk of tendinopathy and tendon rupture in current statin users	833,390 person-years	Trigger finger: current statin users have higher risk, aHR = 1.50 (CI 1.21-1.85) for men and aHR = 1.21 (CI 1.02-1.43) for women. Highest relative risk seen in male users of rosuvastatin (aHR 2.19, CI 1.33-3.62). Shoulder tendinopathy: current users have higher risk, aHR = 1.43 (CI 1.24 -1.65) for men and aHR = 1.41 (CI 0.97-2.05) for women. Achilles tendinopathy: eve users have higher risk, aHR = 1.36 (CI 0.92-2.00) for men and aHR = 1.25 (CI 0.81-1.92) for women. Achilles tendon rupture: aHR = 1.16 in men (CI 0.88-1.54) and aHR = 1.41 in women (CI 0.99-2.27).
Lin et al[3]	Retrospective cohort	III	498,678 participants (25,621 diagnosed with hyperlipidemia)	Incidence of rotator cuff disease in statin-treated *vs* non-treated hyperlipidemic patients	11 years	In hyperlipidemic patients, statin use was associated with a lower RCD risk when compared with no statin use (rosuvastatin HR = 0.41, p <.0001; simvastatin HR = 0.62, p <.0001; others HR = 0.66, p <.0001)

Table II. Studies investigating the use of statins and their possible correlation with repaired tendon re-rupture.

Publication	Study design	Level of evidence	Surgical procedure	Patients' characteristics	Outcome	Follow-up	Main findings
Amit et al[11]	Prospective cohort	II	Arthroscopic repair of isolated postero-superior full-thickness cuff tears after failed conservative treatment	Statin group: 38 DLD patients (15 females, 23 males), mean age 61.7y Control group: 39 non-DLD patients (20 females, 19 males), mean age 60.2y	Pre-op and 12 months post-op: WORC index, CS, ASES score, DASH score, fatty infiltration according to Goutallier and rotator cuff healing according to Sugaya on MRI	12 months	WORC index, CS, ASES score, DASH score significantly improved in both groups compared with baseline (p <.001). No significant difference in post-op scores between groups (p = .14). No significant association of statin use with retear risk (p = .41) or fatty atrophy progression (p = .69)
Zeng et al[34]	Prospective cohort	II	Arthroscopic double-row rotator cuff repair of atraumatic full-thickness tears	134 dyslipidemia patients (79 females, 55 males): 115 in statin users group, 19 in statin nonusers group Mean age 64.4y Mean BMI 25.9 132 control group	Pre-op and 3, 6, 12, 24 months post-op: CS, Oxford shoulder score, UCLASS, VAS	> 24 months	CS, Oxford shoulder score, UCLASS and VAS improved in both groups. No significant difference in post-op scores between statin users and nonusers (p = .099, p = .172, p = .133, p = .776)
Cancienne et al[35]	Retrospective cohort	III	Arthroscopic rotator cuff reapair	Within 6 months of surgery: Cholesterol: 8,163 normal (4,824 statin) 3,535 moderate (1,585 statin) 1,466 high (765 statin) LDL: 5,878 normal (3,812 statin) 5,518 moderate (2,465 statin) 641 high (494 statin) Males/Females: Total cholesterol 6,775/6,389; LDL 6,337/6,000; Triglycerides 6,819/6,411 Age 40y-84y	Ipsilateral revision rotator cuff surgery (included revision repair or debridement)	6 months – 8 years	In moderate and high total cholesterol group, statin non-users had significantly higher rates of revision surgery compared with patients with normal pre-op cholesterol levels (p = .001, p <.0001) In moderate and high LDL levels, statin non-users had significantly increased rates of revision surgery compared with normal pre-op LDL levels (p = .007, p = .020)
Garcia et al[36]	Retrospective cohort	III	Arthroscopic rotator cuff repair after failed nonoperative management	85 patients (54 males, 32 females) Statin group: 33 hyperlipidemia patients Control group: 52 non-hyperlipidemia patients Mean age 62.1y	No retear *vs.* partial retear *vs.* full-thickness retear at post-op ultrasound examination	7.2 months	Hyperlipidemia patients taking a statin medication had significantly higher rates of full-thickness tears (p <.001). Total retear rate was significantly higher compared with non-hyperlipidemia patients (OR = 6.5, p <.001).

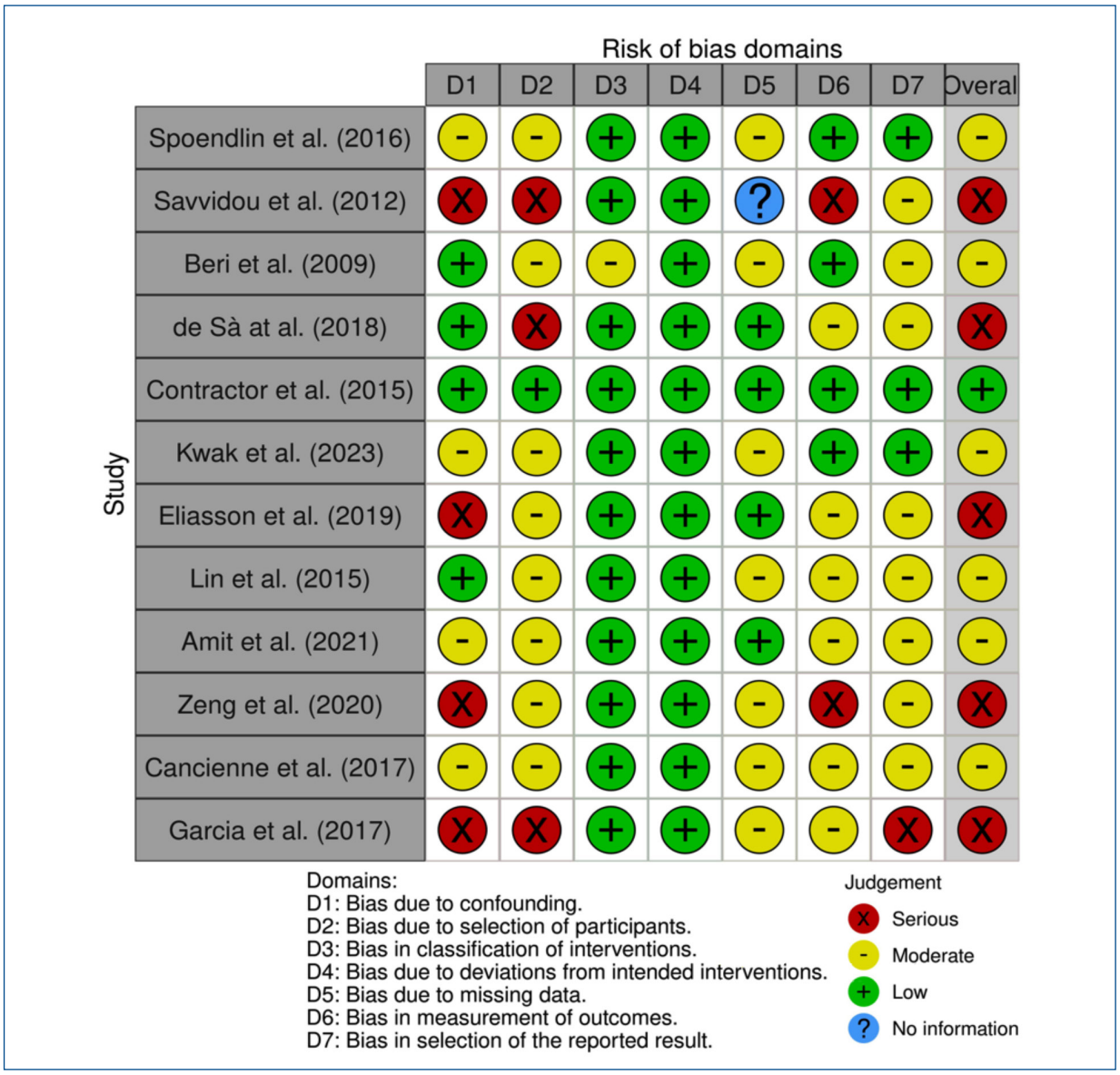


Figure 2. ROBINS-I tool for quality assessment of non-randomized controlled studies.

not find significant differences in either tendon cross-sectional area (p = 0.95). Moreover, a negative correlation between BMI and longitudinal collagen organization (r_s=-0.25, p = 0.042) was reported.

In a retrospective cohort study examining 104,247 sex-matched patients (pulling from a database of 830,883 patients), Contractor et al[31] found no overall association between statin use and tendon rupture after adjusting for confounders. After a mean follow-up of 2.4 years (SD = 1.9), an increased incidence rate of 5.6 per 1,000 patient years in the statin group *vs.* 4.7 per 1,000 patient years was observed; however, after comorbidity index adjusting, the difference between the groups was non-significant with an incidence rate ratio (IRR) of 1.12 (CI 95%, 0.98-1.27). However, isolating different formulations of statins, they found an increased IRR of 2.4 (p<.0001) in atorvastatin users, while simvastatin displayed a protective effect with an IRR of 0.77 (p<.05).

With 13 years of follow-up on 252,306 PS-matched patients from the National Health Insurance Service-National Sample Cohort (NHIS-NSC) database in the Republic of Korea, Kwak et al[32] carried out a retrospective cohort study examining the incidences of trigger finger, radial styloid tenosynovitis, elbow epicondylitis, rotator cuff tendinopathy, and Achilles tendinitis. Statin users displayed a markedly increased risk of developing trigger finger (HR 1.609, 95% CI 1.512-1.714, p<.0001), radial styloid tenosynovitis (HR 1.365, 95% CI 1.247-1.495, p<0.0001), lat-

eral epicondylitis (HR 1.350, 95% CI 1.309-1.393, *p*<.0001), rotator cuff tendinopathy (HR 1.425, 95% CI 1.392-1.459, *p*<.0001), and Achilles tendinitis (HR 1.516, 95% CI 1.380-1.667, *p*<.0001) compared to non-users.

Eliasson et al[33] performed a retrospective cohort study analyzing the occurrence of trigger finger, tendinopathy, or Achilles tendon rupture in 92,933 patients from the Swedish National Patient Register, 37,177 of whom had statin exposure. Male current statin users had a significantly increased multivariable adjusted HR of 1.5 (CI 95%, 1.21-1.85), female 1.21 (CI 95%, 1.02-1.43). Among current statin users, the risk of shoulder tendinopathy was higher in men (HR 1.43; 95% CI 1.24-1.65), whereas the association in women was not statistically significant (HR 1.41; 95% CI 0.97-2.05). HR in Achilles tendinopathy and rupture were not significant in either gender.

Lin et al[3] analyzed a nationwide retrospective cohort of 498,678 individuals identified in 2000 and followed for 11 years, using multivariable Cox proportional hazards models to examine associations of hyperlipidemia and statin use with incident rotator cuff disease, including subgroup analyses for diabetes (*n*=28,391) and hyperlipidemia (*n*=25,621). The findings revealed that utilization of statins was related to a markedly decreased risk of developing rotator cuff disease in comparison to non-use of statins. Multivariate Cox proportional hazards regression demonstrated that statin use conferred a reduction in the hazard for rotator cuff disease development, with the most robust protective effect observed with rosuvastatin (hazard ratio 0.41, 95% confidence interval 0.35-0.49, *p*<.0001).

Statins and operated tendons

Amit et al[11] examined radiographic and clinical outcomes in 77 patients, 38 of whom received statin therapy, after rotator cuff repair in their prospective cohort study. The rates of cuff healing were similar between the two groups, with no significant difference in the relative risk (RR 0.65, CI 95%, 0.24-1.80, *p*=.41). There were also no significant between-group differences in Sugaya grade, Goutallier classification, fatty infiltration, or patient-reported outcome scores like WORC, ASES, Constant-Murley, and DASH.

In the prospective cohort study by Zeng et al[34] examining the influence of dyslipidemia on arthroscopic rotator cuff surgery, 266 patients, 134 of whom had dyslipidemia, were enrolled and followed for 2 years. They found that statin users had a 5% lower worsening in CSS compared to non-users, a 2.1% greater improvement in OXF, a 1.4% lower worsening in UCLASS, and a 0.1% greater improvement in VAS. However, none of these differences were statistically significant.

Cancienne et al[35] implemented a retrospective cohort study analyzing outcomes following primary arthroscopic rotator cuff repair surgery in a cohort of over 30,638 patients, investigating the effects of total cholesterol, LDL, and triglyceride levels. A subgroup analysis stratifying patients by statin use revealed that among statin non-users, patients with high cholesterol exhibited increased rates of rotator cuff revision surgery compared to those with normal cholesterol levels and to statin users with comparable cholesterol levels. For patients with elevated total cholesterol (≥240 mg/dL), statin therapy was associated with a 1.9% absolute reduction in the risk of rotator cuff revision surgery, corresponding to a number needed to treat (NNT) of 54 compared with non-users at similar cholesterol levels. Likewise, in patients with high LDL cholesterol (≥160 mg/dL), statin use yielded a 1.9% absolute risk reduction and an NNT of 53 relative to non-users in the same LDL category.

Garcia et al[36] performed a retrospective cohort study of 85 rotator cuff repair patients, assessing retear rate, with a mean follow-up of 7.2 months. Patients with hyperlipidemia (HL) had a significantly higher rate of rotator cuff repair retears compared to non-HL patients. Specifically, 18.1% of HL patients had a full-thickness rotator cuff retear and 27.2% had a partial-thickness retear, *vs.* 1.9% full-thickness and 9.4% partial-thickness retears in non-HL patients ($p < .001$ for both comparisons). The overall retear rate was 45.5% in HL patients compared to 11.3% in non-HL patients ($p < .001$, odds ratio 6.5, $p < .001$). Retear rates did not differ by individual cholesterol levels (HDL, LDL, total cholesterol, triglycerides), statin dosage, or type of statin medication.

DISCUSSION

The main finding of the present systematic review is that statin use does not universally increase the risk of tendon rupture. Still, certain subgroups, such as female users and atorvastatin users, may be at higher risk. Regarding tendon healing after surgery, statins do not appear to impair recovery in most cases, and they may even provide some protective effects in patients with high cholesterol levels, as hyperlipidemia itself remains a risk factor for poor healing.

Mechanisms by which hyperlipidemia could affect tendon homeostasis and potentially impact healing after tendon repair have been previously proposed. In high-cholesterol environments,

such as in familial hyperlipidemia, lipids accumulate within the tendon's extracellular matrix, compromising various mechanical properties of the tendon, including stiffness and modulus. The mechanisms underlying these cholesterol-related alterations are diverse and include changes in the gene and protein expression of tenocytes, matrix turnover, tissue vascularization, and cytokine production[38]. Accordingly, even statins could impact tendon health and healing. Statins primarily function by reversibly blocking the enzyme HMG-CoA reductase, thereby reducing cholesterol levels. Since mevalonate, a precursor to cholesterol, is also essential for synthesizing other molecules necessary for cellular functions, its inhibition disrupts not only cholesterol production but also other critical cellular processes dependent on this intermediate[39-41].

Several intracellular signaling proteins, such as the subunit of heterotrimeric G-proteins, heme-A, nuclear lamins, and proteins like Ras and Ras-related proteins (e.g., Rho, Rab, Rac, Ral, or Rap), require isoprenoid intermediates for their post-translational modifications and activation[42,43]. These intermediates play an important role in ensuring the proper subcellular localization, anchoring, and intracellular trafficking of these proteins.

To function effectively, Ras and Rho proteins cycle between an inactive GDP-bound state and an active GTP-bound state. These proteins are involved in numerous physiological functions, including cell signaling, cellular proliferation and differentiation, myelination, cytoskeletal regulation, and endocytotic/exocytotic transport[44]. At doses typically used to lower LDL-C levels, statins have been shown to inhibit isoprenylation of Rho and Rho-associated kinases (ROCK)[45].

The Rho/ROCK signaling pathway is integral to cellular processes, such as the regulation of contraction, migration, and adhesion in vascular smooth muscle cells. By inhibiting Rho/ROCK activation, statins increase nitric oxide (NO) bioavailability, a molecule that promotes vasodilation. Statins also block Rac1, a protein associated with cardiac hypertrophy, actin cytoskeleton remodeling, and reactive oxygen species production, all of which are linked to cardiovascular disease mechanisms[46].

Additionally, statins enhance the expression of the peroxisome proliferator-activated receptor (PPAR) and stimulate the transcriptional activity of PPAR in macrophages, contributing to the suppression of lipopolysaccharides involved in inflammatory processes[47].

Finally, matrix metalloproteinases (MMPs), zinc-dependent endopeptidases, facilitate angiogenesis, vascular wall proliferation, vascular remodeling, and extracellular matrix degradation through the migration of vascular smooth muscle cells. The ROCK pathway inhibitor, Y-27632, in conjunction with small interfering RNA, confirmed the essential role of the Rho/ROCK pathway in MMP-2 secretion, as activated by molecules such as endothelin-1 and angiotensin-II[48-51].

We underlined how the evidence synthesized in this review embodies significant heterogeneity, which may partially explain the conflicting findings reported. As shown in Table III, most studies included in this review were rated as having moderate to serious risk of bias, primarily due to potential confounding factors and limitations in participant selection and outcome assessment. This significantly impacts the robustness and generalizability of the conclusions.

In fact, available literature on the effects of statins on native tendons and repaired tendons presents ambiguous and, in some cases, contradictory findings. In particular, several studies have not found a significant association between statin use and an increased risk of tendon ruptures. For example, Spoendlin et al[28] followed a large cohort of over one million patients and, after multivariate adjustment and propensity score matching, did not detect an increased risk of native Achilles or biceps tendon rupture in statin users compared to non-users. Other studies, such as those by Savvidou et al[29] and Beri et al[30], reported a higher incidence of native tendon rupture in statin-treated patients; however, these results did not reach statistical significance.

A notable distinction, however, emerges in the analysis of different subgroups. Beri et al[30] observed that statin use in women is associated with a higher risk of tendon rupture. Moreover, Kwak et al[32] reported an increased risk of inflammatory tendon conditions, such as tenosynovitis and rotator cuff tendinopathy, in patients on statin therapy, especially for specific tendinopathies like trigger finger and Achilles tendinopathy.

In contrast to data suggesting a negative effect of statins on tendons, some studies[3,31] suggest that specific statins like rosuvastatin and simvastatin may have a protective effect, particularly in patients with hyperlipidemia undergoing tendon repair. Indeed, Lin et al[3] found a significant reduction in the risk of rotator cuff disease in statin-treated patients, particularly with rosuvastatin, which showed a more pronounced protective effect. Similarly, Contractor et al[31], analyzing various statin formulations, found a protective effect of simvastatin, while atorvastatin was associated with an increased risk, highlighting potential differences related to individual drugs.

Controversial findings are also observed when analyzing data after surgical repair. Studies such as those by Amit et al[11] and Zeng et al[34] do not report significant differences in postoperative complications or clinical outcomes after rotator cuff repair between patients taking statins and those who do not. However, Cancienne et al[35] observed that, in patients with elevated cholesterol levels, statin use is associated with a reduction in the rate of surgical revision compared to patients with similar lipid levels but not taking statins.

These ambivalent results suggest that the effect of statins on tendons may be modulated by specific variables, such as sex, tendon type, statin formulation, and the presence of comorbidities, including hyperlipidemia and diabetes. In certain contexts, statins appear to offer protective benefits, reducing the incidence of tendinopathies and complications in some types of operated tendons. However, in other cases, they have been associated with an increased risk, especially in specific patient populations[28-32].

Taken together, these findings highlight the complexity of the relationship between statins and tendon health. Apparent discrepancies in the literature may reflect differences in study design, population characteristics, or residual confounding, rather than true pharmacodynamic variability. Further research is needed to clarify whether specific patient factors, such as lipid profile, activity level, or statin type and dose, modulate this association. From a clinical perspective, it may be prudent to preferentially prescribe lower doses or safer statins (e.g., simvastatin, rosuvastatin) in patients at risk for tendon injuries; exercise caution with high-dose atorvastatin, especially in active individuals or patients with previous tendon pathologies and monitor patients engaging in intense physical activity, or those concomitantly treated with corticosteroids, as these factors may exacerbate tendon risk independently of statin use.

Limitations

Nonetheless, the present systematic review has some limitations. First, the predominance of non-randomized studies, which are inherently prone to bias. Additionally, heterogeneity in study designs, populations, and outcomes did not allow us to perform a meta-analysis, hence hindering generalizability and the ability to draw definitive conclusions. The lack of standardization in statin dosage, duration of therapy, and follow-up periods further complicates comparisons. Finally, although some studies adjust for confounding factors, residual confounding may persist, particularly in understanding sex-specific differences and interactions with other medications or conditions, such as level of physical activity and steroid usage. Finally, an important consideration in interpreting these findings is the potential for indication bias. Patients who are prescribed statins typically have underlying dyslipidemia or other metabolic disorders that themselves may predispose to tendon degeneration or impaired healing. Therefore, observed associations between statin use and tendon pathology may, at least in part, reflect the effect of the underlying condition rather than the pharmacologic action of the statin itself. While some studies attempt to control for lipid levels and other confounders, residual confounding remains a significant limitation in most of the included studies. Further prospective, well-controlled studies stratifying results based on statin type, dosage, treatment duration, and patient activity levels are necessary to definitively determine the actual impact of statins on tendon health.

CONCLUSIONS

Statin use is not universally associated with an increased risk of tendon rupture. However, certain subgroups, such as female patients and users of high-dose atorvastatin, may be at elevated risk. Conversely, some evidence points to a possible protective effect of statins like simvastatin and rosuvastatin, particularly in individuals with hyperlipidemia. Overall, the impact of statins on tendon integrity and healing appears to be context-dependent and may be influenced by a range of factors, including patient characteristics, type and dosage of statin, and comorbid conditions, such as hyperlipidemia or concurrent corticosteroid use. Further high-quality, prospective studies are needed to better clarify possible true causative effects, associations, and underlying mechanisms.

Conflict of Interest

The authors declare no conflict of interest related to the writing or the publication of the present study.

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Data Availability

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

Ethics Approval and Informed Consent
Not applicable.

Authors' Contributions
Conceptualization, GA, FV; methodology, FO; formal analysis, FV, FO, MM; data curation, SSDG, PC, GFR, RV; writing–original draft preparation, G.A, FV, FO, MM; writing–review and editing, PC, RV, GFR, BDM, SSDG, EK; supervision, E.K. All the authors conducted a critical review and editing of the final draft. All authors read and approved the final manuscript.

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