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Do statins increase the risk of tendon rupture? A qualitative systematic review

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ABSTRACT

Introduction: Statins are the first-line treatment for atherosclerotic cardiovascular disease (ASCVD) and act by inhibiting HMG-CoA reductase. Possible but rare adverse effects of statins include tendon disorders such as tendinitis and tendon rupture. The purpose of this systematic review is to summarize current studies relating to statins and tendinopathy.

Materials and methods: A search was conducted of studies on the statin-related risk of tendon disorders, published in English until August 2022. It included randomized control trials, experimental studies on human tendon samples and animal tendons, cohort studies, case series, and case reports. The data was then extracted and qualitatively reviewed. The results were tabulated and structured into increased risk, reduced risk, and no effect of statin in tendon disorders.

Results: Out of 48 studies, 17 articles indicated an increased risk of tendon disorders, 6 articles found no correlation between statin use and tendinopathy, 7 articles reported decreased risk, and further 6 articles merely mentioned a tendon disorder and statin use without drawing conclusions. The remaining 12 articles were case reports with bilateral quadriceps tendon rupture as the most mentioned tendon disorder.

Conclusions: Overall, statins did not seem to increase the risk of tendon disorders in a clinical setting. However, in experimental studies, statins were shown to increase the risk. It is presumed that this is due to prescribing statins in hyperlipidemia, which is a risk factor itself for tendon disorders. Controversially, statins exhibit a tendon healing property in *in vitro* conducted studies. Further studies are needed to explore the effects of statins on tendons.

Keywords: statin; hyperlipidemia; tendon; tendinopathy; tendinitis; tendon rupture; risk factor.

INTRODUCTION

Statins are 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, also called HMG-CoA inhibitors, which play an important role in limiting the rate of cholesterol production [1]. These are mainly used in the treatment of dyslipidemia to prevent cardiovascular events such as stroke, myocardial infarction, and atherosclerosis [2]. Statins have been established as the first-line treatment of atherosclerotic cardiovascular disease (ASCVD), as they stabilize existing plaques, reduce plaque formation, improve endothelial function, inhibit platelet thrombus formation, and exhibit anti-inflammatory activity [3, 4]. The first stain, lovastatin, was introduced by Merck in 1984 and was approved by the Food and Drug Administration (FDA) in September 1987 as the first commercial statin. Since then, 5 more statins have been approved by the FDA: simvastatin (1992), pravastatin (1989), atorvastatin (1996), fluvastatin (1994), pitavastatin (2003), and rosuvastatin (2003) [5]. Major adverse effects of statins include myopathy, rhabdomyolysis, and rarely, liver disorder [6, 7, 8, 9]. Less common adverse effects are tendon problems, such as tendinopathy, tendinitis, and even tendon ruptures.

Controversy remains whether statin use produces tendinopathy, as statins are mostly prescribed to patients with dyslipidemia, which itself is a predisposing factor for tendon disorders. Some case-control studies suggest the involvement of statins in tendon pathology, and reports on tendinopathy resolution after statin discontinuation may support the role of statins. However, there are also observations suggesting a lack of association between statin administration and tendon disorders. The review summarizes available information about statins and their role in tendinopathy, which, due to reduced mobility and dissatisfaction, may have a significant impact on the quality of life.

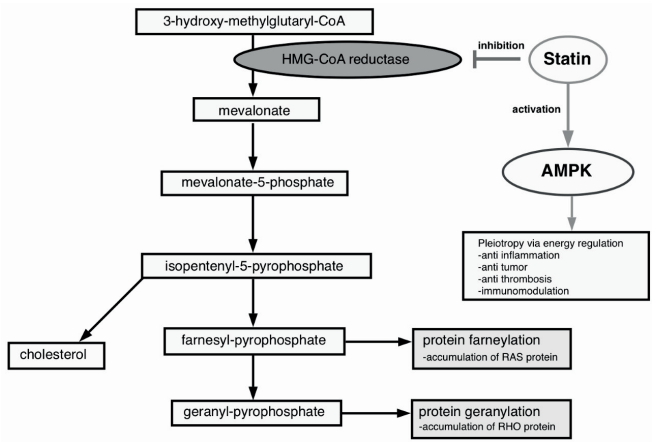
Mechanism of action

The rate-limiting step in cholesterol synthesis is the conversion of HMG-CoA to mevalonate with HMG-CoA reductase as the catalyzing enzyme. Therefore, inhibiting HMG-CoA reductase with a statin reduces cholesterol production, depleting the intracellular supply of cholesterol. This depletion of intracellular cholesterol leads to an increase in the number of cell surface low-density lipoprotein (LDL) receptors, resulting in the internalization of circulating LDL. As a result, bloodstream cholesterol is reduced through decreased production of cholesterol and increased uptake of circulating cholesterol [10].

Among statins, pitavastatin, rosuvastatin, and atorvastatin exhibit the most potent cholesterol-lowering activity, followed by simvastatin, pravastatin, lovastatin, and fluvastatin, in descending order. Statins are metabolized primarily in the liver, with a minor portion metabolized in other organs such as the intestine and kidney, and are mainly excreted via bile and feces.

In addition, statins have been found to be involved in post-translational protein modification via prenylation. By decreasing mevalonate synthesis, statins reduce the production of mevalonate-5-phosphate, isopentenyl-5-phosphate, farnesyl-pyrophosphate (FPP), and geranylgeranyl-pyrophosphate (GGPP) [11]. Farnesyl-pyrophosphate and GGPP are important intermediates in farnesylation and geranylation. Proteins such as rat sarcoma (Ras) protein and Ras-like proteins including ρ factor (Rho), Ras-associated binding (Rab), Ras-related protein (Ral), and receptor-associated protein (Rap) play essential roles in covalent attachments and intracellular signaling of membrane proteins [12]. The prenylation of Ras protein is FPP-dependent, while Rho relies on GGPP in endothelial cells. Inhibition of these substrates by statins, leads to the accumulation of inactivated Ras and Rho in the cytoplasm. This accumulation induces changes in the vascular wall and actin cytoskeleton of cells, leading to disruptions in intracellular signaling, mRNA stability, and gene transcription [13, 14].

Furthermore, statins activate adenosine monophosphate-activated protein kinase (AMPK), which serves as an energy regulator in eukaryotes. Adenosine monophosphate-activated protein kinase regulates cell growth by phosphorylating and controlling glucose uptake in specific tissues such as muscle and adipose tissue. The literature also reports additional pleiotropic effects of AMPK, including the regulation of p53 tumor suppressor, cyclin-dependent kinase inhibitor, and p21WAF1 activities, which mediate cell growth regulation [15, 16]. Therefore, studies have suggested that statins regulate pleiotropy not only as cholesterol-lowering drugs but also as anti-inflammatory, anti-tumor, anti-thrombotic, and immunomodulatory agents [16, 17] – Figure 1.



HMG-CoA – 3-hydroxy-3-methylglutaryl-coenzyme A; RAS – rat sarcoma; RHO – Ras homology

FIGURE 1. Effect of statin on adenosine monophosphate-activated protein kinase (AMPK) and protein prenylation

Mechanism of tendon disorders in dyslipidemia and obesity

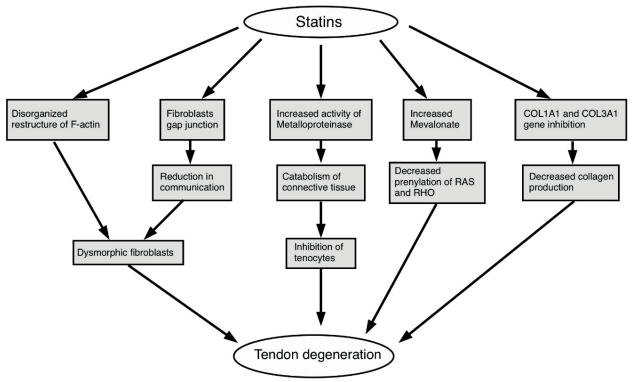
Tendons, which are made up of fibroelastic connective tissue, can be influenced by statins and hyperlipidemia. The main component of tendons is type III collagen fibers produced by active tenoblasts and fibrocytes [18, 19, 20]. With age, tenoblasts become inactive and therefore increase the risk of rupture [20]. Tendons are adapted to long-lasting, low-oxygen environments without major enzymatic workload adaptation [21, 22]. Therefore, blood is sparsely supplied by the intrinsic and extrinsic vascular system from the muscle/bone and paratenon, respectively [18, 23, 24].

Dyslipidemia and obesity are known risk factors for tendon disorders, as cholesterol accumulates in the tendon. This accumulation causes disruption of the extracellular matrix due to an increased inflammatory process and decreased production of collagen. Pro-inflammatory adipokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, IL-8, leptin, resistin, fatty acid binding protein 4 (FABP4), visfatin, chemerin, adiponectin, and omentin-1, as well as fibroblast growth factor 21 (FGF21) are involved in the process [25]. It has been suggested that adipokines are responsible for the stimulation and differentiation of monocytes into macrophage foam cells, the modulation of natural killer cells, and the enhancement of pro-inflammatory cytokines production. The dysregulation of adiponectin leads to regulatory failure of IL-10, which is responsible for the inhibition of metalloproteinases, important enzymes in catabolic changes in the connective tissue [26]. Additionally, adiposity changes the functional state of macrophages – the transformation from their usual M2 state into pro-inflammatory M1 state, which leads to increased cytokine production and release [27]. Furthermore, increased infiltration of pro-inflammatory immune $CD8^+$ cells and a decrease in anti-inflammatory $CD4^+$ T-cells further impact inflammatory processes in the tendon [28, 29, 30, 31].

Mechanism of rupture with statins

In the literature, it has been hypothesized that statin administration might be a risk factor for tendon rupture. The precise mechanism of tendon degeneration due to statins is suggested to be due to increased production of degrading metalloproteinases. Experimental findings showed a different composition of the extracellular matrix and increased metalloproteinase activity, which is implicated in the degradation of connective tissue, leading to changes in the extracellular matrix [32]. An increase in metalloproteinase activity favors the turnover rate towards catabolism and therefore decreases tensile strength [33]. Histologically, collagen fibers appear to be disrupted, with a decreased amount of collagen with the use of statins. Furthermore, collagen fibers appear less organized, with small gaps in between them. Kuzma-Kuzniarska et al. reported possible mechanisms of tendinopathy produced by statins, describing reduced expression of *COL1A1* and *COL3A1*, which are responsible for the production of collagen 1 and collagen 3, respectively. Furthermore, reduced intercellular communication via gap junctions resulting from inactivation of

active fibroblasts and their conversion to dysmorphic rounder cells was demonstrated. The above functional evolution was associated with tenoblastic cell structure disruption expressed by the disorganized restructuring of F-actin, an important building block of the cytoskeleton, which was observed only in the peripheral cell structures. Lastly, the study revealed that statins affected protein prenylation through a reduction in mevalonate, the main product of the reaction catalyzed by HMG-CoA, which is inhibited by statins. Mevalonate prevents the reduction of prenylation through activation of the *Rap1a* gene expression. Therefore, it is suggested that statins lead to an inhibition in the growth, differentiation, and migration of tenocytes under statin exposure, which decreases production rates of the extracellular matrix [34]. Most commonly, the reported tendon ruptures due to statin administration refer to the Achilles tendon, quadriceps tendon, tendons of the rotator cuff, biceps tendons, and the tendon of the finger [13] – Figure 2.



RAS – rat sarcoma; RHO – Ras homology

FIGURE 2. Effect of statins on tendon degeneration

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement 2020 were used to design this systematic review. The primary objective of this systematic review is to determine the association between statins and tendon disorders based on the current evidence. The secondary objective includes the analysis of the relationship between specific statins, as well as the dose, and the development of tendon pathology.

Literature search

The databases Scopus, Medline, Embase, and Web of Science were searched until August 10th, 2022, to identify research papers on the association between statins and tendon problems such as tendinitis, tendinopathy, and tendon rupture. A Boolean search was conducted using the following strings "(tendon AND *statin)", "(tendon rupture AND *statin)", "(tendinitis AND *statin)" and "(tendinopathy AND *statin)". Only articles published in English were included and no specific time frame was set. The inclusion criteria encompassed all types of original research involving humans, animals, *in vivo* and *in vitro.* This included randomized controlled trials, case reports, cadaveric studies, retrospective and prospective cohort studies, and case series. Review articles such as narrative reviews, systematic reviews, and meta-analyses were excluded. The titles and abstracts of the identified articles were then screened to determine their relevance to this systematic review. Full-text articles were obtained and reviewed by the researchers. The search was conducted by a principal investigator and reviewed by a co-investigator. Data extraction and tabulation included information on the number of patients, age, sex, diagnosis, statin dosage, and outcomes. For articles that did not provide numerical data, a qualitative analysis was performed.

Search results

The initial search across Scopus, Embase, Medline, and Web of Science databases yielded a total of 1601 articles. Among these, 1041 were from Scopus, 228 from Embase, 213 from Medline, and 119 from Web of Science. After removing duplicates, 1052 unique articles were left for further screening. During the title and abstract screening phase, 588 articles were excluded as they were not relevant to the topic of tendon disorders and statins, resulting in 464 articles for full-text review. Further exclusions were made during the full-text review process for articles that did not meet the inclusion criteria related to tendon or statin topics. Ultimately, a total 48 articles were included in this systematic review. Further articles from other sources were not identified (Fig. 3).

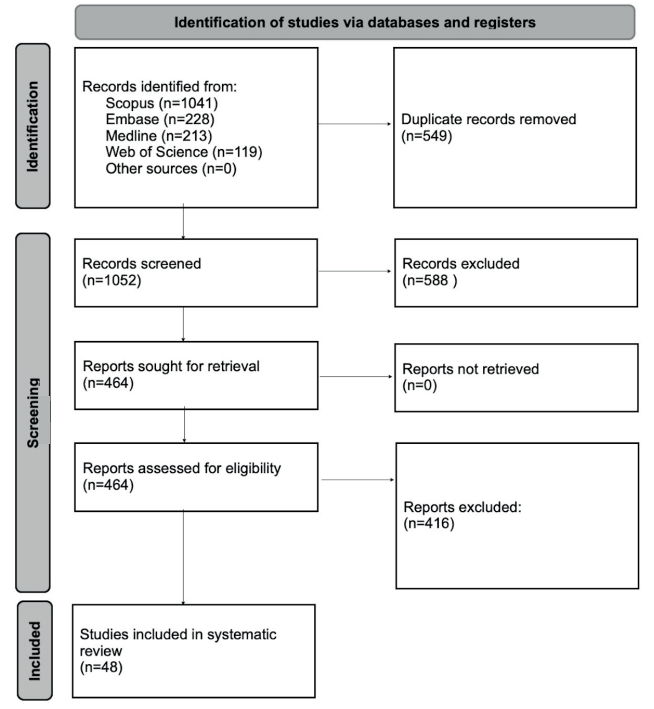


FIGURE 3. PRISMA 2020 flow chart for systematic review of statins as a risk factor for tendinopathy, tendinitis, and tendon rupture

RESULTS

Out of the 48 articles included in the systematic review, 45 different first investigators contributed to the research, and these articles were published in 40 different journals. Among the included articles, 12 (25%) articles were presented as case reports [35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46], 23 (47.9%) were clinical studies (either as cohort or database studies) and 13 (27.1%) were experimental studies [32, 34, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80]. Out of the 13 experimental laboratory studies, 11 were conducted on animals. The earliest article included in the review was published in 2004, while the most recent was published in 2022. The included articles showed a high degree of heterogeneity, which precluded the possibility of conducting a meta-analysis. It is important to note that some of the studies included in the review did not specifically focus on statins in relation to tendon disorders, but rather mentioned statins among other risk factors.

Article results and type of article

All 12 case reports that were analyzed were excluded from the systematic review as they presented correlations between statins and tendon disorders in a report-style format.

Out of the remaining 36 articles, 17 (47.2%) articles suggested statins as a risk factor for tendon disorders, 6 (16.7%) reported no correlation between statins and tendon disorders, and 7 (19.4%) found a reduction in the risk of tendon disorders with statin medication. Additionally, 6 (16.7%) articles mentioned tendon disorders without specifically focusing on the risks associated with statin usage.

Among the 17 articles suggesting statins as a risk factor, 8 (47.1%) were experimental studies, including 6 studies conducted on animal tendons and 2 on human tendon samples. The other 9 (52.9%) articles were clinical studies, with 3 utilizing population-based databases and 6 studies being cohort studies.

The 6 studies that showed no correlation of statins as a risk factor for tendon injuries consisted of 5 (83.3%) clinical studies, including 3 population-based databases, 1 questionnaire study, and 1 cohort study. The remaining study was an experimental study conducted on animal tendons.

In the group of 7 implicating statins as a form of prevention for tendon disorders, 3 (42.9%) were clinical studies, with 1 being a population-based database and 2 being cohort studies. The remaining 4 (57.1%) articles were experimental studies conducted on animal models.

Lastly, the 6 studies where authors mentioned statin usage without reporting on the risk evaluation of tendon disorders were all clinical studies, with 1 being a population-based database.

The summarized findings from these articles are presented in Table 1.

CASE REPORTS

Of the 12 case reports analyzed, 10 of them reported the sex of the patients. Among these reports, there were 10 males and 3 females. The average age of all 9 case reports was 51.4 ±8 years (median: 53, IQR: 46–56, range: 34–65). Overall most commonly described was the rupture of the quadriceps tendon, which was observed in 5 of the 9 cases. Further relevant tendons that were involved included the Achilles tendon and distal biceps tendon (Tab. 2).

Clinical and experimental studies

Table 3 provides a summary of the results from the clinical and experimental studies. Out of the 17 studies that reported an increased risk for tendon disorders, 8 were conducted as laboratory studies, with 4 being *in vitro* addition of statin and 4 being *in vivo* addition of statin. It is worth noting that the *in vivo* experimental studies on animals used significantly higher dosages of statins compared to prescribed dosages for humans. Dosages ranging 20–80 mg/kg of any statin were used in 3 out of 5 studies, whereas the prescribed statin dosages for a whole human body per day typically range 20–80 mg.

In the section discussing the reduced risk of tendon disorders, 4 experimental studies were conducted, with 3 of them

TABLE 1. Tendency and type of article

	Higher risk	No correlation	Lower risk	Mentioned in the study*	Case reports
Total number	17	6	7	6	12
Clinical	9	5	3	6	–
database	3	3	1	1	–
questionnaire	0	1	0	0	–
cohort	6	1	2	5	–
Experimental	8	1	4	0	–
animal	6	1	4	0	–
human	2	0	0	0	–

* In these studies, statins were mentioned in relation to tendon disorders but the authors did not provide any specific conclusions.

TABLE 2. Case reports evaluation

Reference	Diagnosis/assessment	Dosage with time*	Co-morbidities/co-medications
Govindu et al. 2019 [35]	bilateral distal quadriceps rupture/ clinical examination, X-ray and MRI	A	diabetes mellitus, CKD, hypertension, hypothyroidism, levothyroxine, aspirin, atorvastatin, insulin, metoprolol, amlodipine, omeprazole, sevelamer
Gowdar and Thompson 2020 [36]	partial gastrocnemius rupture	A – 40 mg for 15 years	no risk factors
	distal biceps tendon rupture	A – 80 mg for 1 year	
	second partial gastrocncemius rupture	A – 40 mg for 1 year	
	partial tendon rupture in elbow	R – 10 mg for 1 year	
	partial tendon rupture in wrist	R – 40 mg for a few months	
	wrist pain	R – 10 mg for a few months	
Patel and Carayannopoulus 2016 [37]	bilateral distal quadriceps rupture/ clinical examination X-ray and MRI	A for 10 months	no risk factors
Cano Cevallos et al. 2019 [38]	tendon rupture in lower limb/clinical examination and MRI	S – 10 mg	hydrochlorothiazide, amlodipine, benazepril, naproxen, ferrous sulfate, multivitamins, calcium supplements, gemfibrozil (3 weeks)
Celik et al. 2012 [39]	bilateral distal quadriceps rupture/ clinical examination and MRI	R for 4 years	valsartan, hydrochlorothiazide, acetylsalicylic acid
Carmont et al. 2009 [40]	bilateral Achilles tendon rupture/ clinical examination and ultrasound	S – 40 mg for 12 weeks	family history of cardiac problems
Pullatt et al. 2007 [41]	left biceps tendon rupture, right biceps pain/MRI	P and ultimately S + E for 4 months	no risk factors
Kearns and Singh 2016 [42]	bilateral patellar tendon rupture/ clinical examination and X-ray	S – 40 mg	ischemic heart disease, bisoprolol, eplerenone, ramipril, aspirin
Nesselroade and Nickels 2010 [43]	bilateral distal quadriceps rupture/ clinical examination and ultrasound	A – 20 mg for 3 years	no risk factors
Chazerain et al. 2001 [44]	tenosynovitis of finger extensor tendon/clinical examination	S – 10 mg for 2 months	hypercholesterolemia, arterial hypertension, angina
	acute tendinitis of right tibialis anterior tendon/clinical examination and ultrasound	A – 20 mg for 2 months	hypercholesterolemia
	acute tendinitis of right Achilles tendon/clinical examination and ultrasound	S – 20 mg for 2 weeks	hypercholesterolemia
	acute tendinitis of both Achilles tendon/clinical examination, ultrasound and MRI	A – 40 mg for 23 years and A – 80 mg for 1 month	hypercholesterolemia, angina, polymyalgia rheumatic, erectile dysfunction due to aortic aneurysm
Moniri et al. 2018 [45]	left Achilles tendon rupture and bilateral tendinitis/surgical repair for left Achilles tendon rupture	R – 5 mg for 7 months, R – 2.5 mg for 7 weeks and P – 20 mg for 20 mg	hypercholesterolemia, hypertension
Rubin et al. 2011 [46]	bilateral quadriceps tendon rupture/ clinical examination, ultrasound, intraoperative repair	S – 40 mg for 2 years (in total S for 4 years)	hypercholesterolemia, hypertension

A – atorvastatin; S – simvastatin; R – rosuvastatin; P – pravastatin; E – ezetimibe; MRI – magnetic resonance imaging; CKD – chronic kidney disease
* Values for the dosage are prescribed per day.

being *in vitro* studies. Among the clinical studies, many of them observed the occurrence of tendon disorders without specifying the locations. However, some specific locations included the Achilles tendon, rotator cuff, distal biceps tendon, and finger tendons.

Eliasson et al. conducted a study that differentiated the risk of statin usage by calculating hazard ratios. The study showed that fluvastatin and rosuvastatin had higher hazard ratios for trigger finger than other statins, with hazard ratios of 2.55 and 1.89 (95% confidence interval – CI) in women and 2.62 (95% CI)

TABLE 3. Clinical and experimental evaluation

Reference	Type of study	Cohort/ sample size	Number of tendon disorders	Dosage*	Conclusion	Diagnosis/assessment
Chang et al. 2022 [47]	clinical/human	706767	–	–	increased risk	tendon disorder
Wang et al. 2021 [48]	clinical/human	151	3	A – 40 mg for 2 years	increased risk	tendon disorder/MRI
Eliasson et al. 2019 [32]	clinical/human	833390	1056	–	increased risk	trigger finger
			2059	–	increased risk	shoulder tendinopathy
			308	–	increased risk	Achilles tendinopathy
Cong et al. 2018 [49]	experimental/ mouse/*in vitro*	23	–	–	increased risk	–
Kaleağasıoğlu et al. 2017 [50]	experimental/ rat/*in vivo*	49	–	S – 20 mg/kg, S – 40 mg/kg, A – 20 mg/kg, A – 40 mg/kg, R – 20 mg/kg, R – 40 mg/kg for 3 weeks	increased risk	–
Eliasson et al. 2017 [51]	experimental/ human/*in vitro*	6	–	–	increased risk	–
Oliveira et al. 2017 [52]	experimental/ rat/*in vivo*	25	–	A – 20 mg, A – 80 mg, S – 20 mg, S – 80 mg for 2 months	increased risk	–
Tsai et al. 2016 [53]	experimental/ rat/*in vitro*	–	–	–	increased risk	–
Kuzma-Kuzniarska et al. 2015 [34]	experimental/ human/*in vitro*	–	–	–	increased risk	–
de Oliveira et al. 2013 [54]	experimental/ rat/*in vivo*	50	–	A – 20 mg, S – 20 mg, A – 80 mg, S – 80 mg for 2 months	increased risk	–
Hoffman et al. 2012 [55]	clinical/human	147789	2635	–	increased risk	tendon and joint disorder
Savvidou and Moreno 2012 [56]	clinical/human	104	104	–	increased risk	spontaneous distal biceps tendon rupture/post--surgical intervention
Marie et al. 2008 [57]	clinical/human	96	96	A – 26 mg, S – 18 mg, P – 22 mg, F – 40 mg, R – 10 mg	increased risk	tendon rupture and tendinitis/clinical examination, X-ray, ultrasound and MRI
Ekhart et al. 2016 [58]	clinical/human	15	2	A – 23 mg, F – 20 mg, P – 15 mg, R – 20 mg, S – 40 mg	increased risk	tendon rupture
de Oliveira et al. 2015 [59]	experimental/ rat/*in vivo*	–	–	–	increased risk	–
Beri et al. 2009 [60]	clinical/human	93	93	–	increased risk	tendon rupture
Rafi et al. 2016 [61]	clinical/human	611	611	A, S, R, P, F, L, Pi	increased risk	tendon rupture
Morales et al. 2019 [62]	clinical/human	1351780	4836	–	no correlation in risk	tendon rupture
de Sá et al. 2018 [63]	clinical/human	33	33	–	no correlation in risk	structural changes of Achilles tendon/ultrasound

TABLE 3. Clinical and experimental evaluation

Reference	Type of study	Cohort/ sample size	Number of tendon disorders	Dosage*	Conclusion	Diagnosis/assessment
Choi et al. 2018 [64]	experimental/ rat/*in vivo*	30	–	S – 20 mg/kg for 3 months	no correlation in risk	–
Bakker et al. 2017 [65]	clinical/human	4460	1697	–	no correlation in risk	tendon-, ligament-, and muscle injury
Spoendlin et al. 2016 [66]	clinical/human	539039	–	S < 20 mg, S > 20 mg, S > 40 mg	no correlation in risk	tendon rupture
Contractor et al. 2015 [67]	clinical/human	34749	–	–	no correlation in risk	tendon rupture
Weng et al. 2022 [68]	experimental/ rat/*in vitro*	60	–	–	reduced risk	–
Amit et al. 2021 [69]	clinical/human	38	38	–	reduced risk	rotator cuff tendon/MRI
Coombes et al. 2019 [70]	clinical/human	33	18		reduced risk	tendon properties/ ultrasound and shear wave electrography imaging
Jeong et al. 2018 [71]	experimental/ rat/*in vitro*	-	–	–	reduced risk	–
Dolkart et al. 2014 [72]	experimental/ rats/*in vivo*	48	–	A – 20 mg/kg	reduced risk	–
Oka et al. 2013 [73]	experimental/ rabbit/*in vitro*	42	–	–	reduced risk	–
Lin et al. 2015 [74]	clinical/human	1000000	26664	–	reduced risk	rotator cuff disease
Lee et al. 2020 [75]	clinical/human	159	2	P – 40 mg for 120 months	not mentioned	tendon rupture
Kheloufi et al. 2017 [76]	clinical/human	72	5	–	not mentioned	tendon pain
Carnovale et al. 2016 [77]	clinical/human	1073	–	–	not mentioned	tendon rupture
Choi et al. 2010 [78]	clinical/human	1093262	–	–	not mentioned	tendon rupture
Mignini et al. 2008 [79]	clinical/human	36	–	L – 40 mg	not mentioned	tendon disorders
Ballantyne et al. 2004 [80]	clinical/human	153	1	R – 40 mg or 80 mg	not mentioned	Achilles tendon rupture

A – atorvastatin; S – simvastatin; R – rosuvastatin; P – pravastatin; F – fluvastatin; L – lovastatin; Pi – pitavastatin; MRI – magnetic resonance imaging
* Values for the dosage prescribed per day.

for rosuvastatin in men. In shoulder tendinopathy, rosuvastatin had the highest hazard ratio of 1.46 (95% CI). The study also showed that the risk of tendon injury associated with statin usage is reversible, as the hazard ratios were similar to the reference value (between 0.82–1.33 95% CI) for individuals who discontinued statin use more than 2 years earlier [11, 32].

DISCUSSION

This systematic review shows the current information about statins as a risk factor for tendon disorders. The most commonly diagnosed tendon disorder reported in the included studies was ruptures, which is easier to diagnose compared to tendinopathy. It is worth noting that tendinopathy, which may have milder symptoms such as light pain, could be underdiagnosed as patients may only report significant pain, leading to potential underestimation of its prevalence.

The number of studies suggesting an increased risk of tendon disorders with statin use is similar to the number of studies reporting no correlation or reduced risk, with 16 and 13 articles, respectively. Among the articles indicating an increased risk, only 8 (50%) of 16 articles in the group indicating a higher risk are clinically based, while in the group of articles that showed no correlation, 5 (83%) out of 6 were clinical studies. A substantial number of studies presenting statins as the increased risk factor were experimental studies, and therefore did not have direct clinical relevance, as experimental studies are performed in the laboratory mostly with animal specimens and at higher dosages compared to clinical studies [50, 54, 64]; yet they showed the potential risk of tendon disorders. In a clinical setting, statins might even reduce the risk of tendon disorders. Case reports suggest a correlation between statins and tendon rupture, yet in these case reports, other comorbidities

and medications were present, which might be risk factors for tendon disorders. Based on articles showing an increased risk of tendon disorder, we believe that statins themselves, as drugs, are potent agents acting negatively on the tendon. However, they treat dyslipidemia, which is also a significant metabolic problem causing tendon disorders. Statins acting on dyslipidemia via their other pleiotropic effects, especially within atherosclerotic plaques, reduce cardiovascular risks. This effect outweighs their potential direct negative effects on tendons. Additionally, in experimental studies, animals were exposed to very high doses of statins (in comparison to clinical recommendations) which suggests the statin dose--dependent risk of tendon disorders. This has also been shown by Eliasson et al. in terms of the hazard ratio [32]. Therefore, it can be suggested that statins are direct risk factor for tendinopathy, but in patients with hyperlipidemia, the agents can reduce the risk of tendon disorders, as hyperlipidemia is the predominant risk factor. In some experimental *in vitro* studies, it was shown that statins have a biphasic mode of action. In low dosages, statins increase angiogenesis, leading to the increased potential of healing, and in the high-dose/concentration range, they produce opposite effects. In murine models, low-dose cerivastatin or atorvastatin therapy (0.5 mg/kg/day) enhanced inflammation-induced angiogenesis, whereas at high doses of the statins (2.5 mg/kg/day), it was significantly inhibited [81]. In animal models, endothelial cells revealed that low doses of atorvastatin resembling the plasma concentrations in patients on chronic statin therapy (0.01–0.1 mM) promoted endothelial cell migration and angiogenesis. In contrast, higher concentrations of atorvastatin (40.1 mM) produced anti-angiogenic effects [82]. Antiangiogenic effects at high concentrations were associated with the decreased endothelial release of vascular endothelial growth factor and increased endothelial apoptosis and were reversed by geranylgeranyl pyrophosphate [73, 83].

Case reports on statin discontinuation in patients with tendinitis may support a causative relationship between statins and tendinopathy. In patients diagnosed with tendinosynovitis associated with a simvastatin dose of 10 mg/day for 2 months, and acute tendinitis produced by simvastatin (20 mg/day for 1 month) or atorvastatin (40, then 80 mg/day for 2 months) withdrawal of statin therapy lead to recovery within 6 weeks to 2 months. These reports do suggest that discontinuation of statin therapy can lead to the recovery of tendinopathy [44].

One of the main strengths of this systematic review is the selection of broad search terms in order to find every study concerning tendons and statins. An additional strength of the systematic review is the inclusion of experimental studies on human tissues and animals. This allows for the observation of potential properties of statins on tendons, regardless of systemic consequences, as doses can be chosen in a wider range that would not be applied in a clinical setting. Therefore, investigations on the potential risks of statins as agents producing tendon disorders could be carried out in subjects/animals/tissues without prescription indications of those drugs. As already stated above, statins might reduce cardiovascular risk when administered in hyperlipidemia according to clinical guidelines. However, based on clinical observations (due to co-morbidities and drugs co-medicated with statins), the dose-dependent responses when statins are considered as risk factors of tendinopathy were not established, contrary to dose-dependent hypolipemic responses.

The presented systematic review has several limitations. There are no randomized controlled trials available, and only a small number of lower-quality studies were included in the analysis. The analyzed studies included patients attending different types of health care units, information was withdrawn from different types of databases (e.g. hospitals, insurance companies), subjects were exposed to various statins and in some reports doses were not provided. There is also limited information available for other clinical variables such as co-morbidities and co-medications, and there are differences in the follow-up time. These factors can potentially impact the outcomes of the review.

CONCLUSIONS

Overall, statins do not appear to be highly potent risk factors for tendon disorders in clinical settings, as they are primarily prescribed in hyperlipidemia, which itself is a risk factor for tendon disorders. Experimental studies have shown that statins have both potential risks of tendinopathy and healing potential. Whether these actions are dose-dependent remains undefined. However, experimental studies suggest that lower doses of statins result in healing effects, while high doses increase the risk of tendinopathy. Clinical studies do not provide strong evidence for these experimental findings, as they are confounded by many factors such as co-morbidities, co-medications, and the level of physical exercise which make the observations inconclusive.

Considering the importance of clinical studies and the common occurrence of hyperlipidemia as a risk factor for tendon pathology, it is still suggested to treat patients with statins. However, cases with severe tendon pathologies should be evaluated on an individual basis.

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