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Current Research on the Influence of Statin Treatment on Rotator Cuff Healing

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Rotator cuff tears are a condition characterized by damage to the muscles and tendons that connect the scapula and humerus, which are responsible for shoulder rotation and arm lifting. Metabolic factors such as diabetes, thyroid disease, high cholesterol, vitamin D deficiency, obesity, and smoking have been associated with an increased risk of rotator cuff tears. Interestingly, patients with hyperlipidemia, a condition characterized by high levels of cholesterol and other fats in the blood, have been found to have a higher incidence of rotator cuff tears and breakdown of tendon matrix. As a result, statin therapy, which is commonly used to lower cholesterol levels in hyperlipidemia, has been explored as a potential treatment to improve clinical outcomes in rotator cuff tears. However, the results of preclinical and clinical studies on the effects of statins on tendon healing in rotator cuff tears are limited and not well-defined. Moreover, since hyperlipidemia and rotator cuff tears are more prevalent in older individuals, a literature review on the efficacy and safety of statin therapy in this population is needed.

Keywords: *Statin, Rotator cuff, Tendon healing, Lipid-lowering therapy, Hyperlipidemia*

Rotator cuff muscles and tendons can be damaged or torn due to various reasons, such as shoulder overuse, trauma, or age-related degenerative diseases.[1] Approximately 20.7% of people experience a full-length tear according to population-based studies.[2] Rotator cuff tears (RCTs) can cause severe shoulder pain and limit motor function, which can significantly impact an individual's daily life. Recent studies involving 5,856 patients have shown that hypercholesterolemia, with a total cholesterol level of 5 mmol/L or higher, is associated with a 1.5-fold increased risk of upper extremity tendon injury and a 2.5-fold increased risk of metabolic syndrome.[3] In another study, individuals with a body mass index (BMI) % ≥ 75%, which is considered a risk factor for hyperlipidemia, exhibited distinct differences in the composition of the extracellular matrix in tendons compared to those with a lower BMI.[4] These studies suggest a strong causal relationship between hyperlipidemia and RCTs. Therefore, it is important to consider treatment strategies that address the effects of hyperlipidemia to improve clinical outcomes in rotator cuff treatment.

Statins are a class of lipid-lowering drugs used by 25 million patients worldwide to lower blood cholesterol levels. They are the most commonly used drugs to lower cholesterol levels and reduce the risk of heart disease by inhibiting an enzyme called 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase) involved in cholesterol production in the liver.[5] However, there is a lack of research on the direct effects of statin-induced low-density lipoprotein cholesterol (LDL-C) lowering on muscle degeneration, pain, inflammation, and overall healing process in rotator cuff treatment. The effectiveness and safety of statins in this context are not well-defined. Therefore, this review aims to identify the latest research trends in rotator cuff tendon healing and report the benefits and potential risks of statin use.

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HYPERLIPIDEMIA AND RCTs

Hypercholesterolemia is a condition where there is an excessive amount of cholesterol in the form of lipids present in the bloodstream. It is a common condition that affects more than 25% of the American population, and it is defined as having a total serum cholesterol level of 240 mg/dL or higher.[6] Familial hypercholesterolemia (FHC) is a specific type of hypercholesterolemia that is inherited from one or both parents. This condition results in reduced or dysfunctional activity of the LDL receptor, which is responsible for the liver's absorption and breakdown of lipids.[7] As a result, individuals with FHC have significantly raised serum cholesterol levels, often reaching up to 1,000 mg/dL, which is well above the healthy cholesterol level of 200 mg/dL. Homozygous FHC is a rare form of FHC that affects 1 in 1 million individuals, while heterozygous FHC is more common and affects 1 in 500 individuals worldwide.[7]

Metabolic disorders, like FHC, can result in an increase in pro-inflammatory cytokines and the destruction of the extracellular matrix through matrix metalloproteinases.[8] The presence of pro-inflammatory monocytes, along with inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-8, and IL-6, can lead to a decrease in collagen synthesis and an altered extracellular matrix.[8] In tendinopathy, downstream activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), TNF-α, IL-1, and pattern recognition receptors in tendon fibroblasts is increased. This activation can contribute to chronic inflammation and tissue damage in the tendon.[8,9] Additionally, the production of IL-6 can stimulate T-cell and macrophage activation, further exacerbating inflammation in the presence of TNF-α. TNF-α and IL-6 can also stimulate myocyte apoptosis, leading to dysregulation of intramuscular protein catabolism and regeneration pathways.[10] The inflammatory effects that occur at the molecular and cellular level can potentially lead to inferior biomechanical properties and impaired tendon healing in vivo.

Studies investigating the effects of high cholesterol on tendon mechanics in small and large animal models have shown that hypercholesterolemia can have varying effects on different tendons. Specifically, hypercholesterolemia was found to increase the stiffness and modulus of elasticity of the supraspinatus tendon in rats and monkeys, while the biceps brachii muscle of pigs showed decreased stiffness and modulus.[11] These differences in mechanical outcomes may be due to differences in the internal and external loading environments of the two tendons.[11] Additionally, hypercholesterolemia has been shown to have detrimental effects on native tendon healing in supraspinatus rat tendon and patellar mouse tendon injury models, leading to reduced elastic modulus and normalized maximal stress in mice and decreased normalized spasticity 4 weeks after injury in mice.[12] These findings suggest that hypercholesterolemia can negatively impact tendon mechanics and healing, which may have implications for the management of tendon injuries in patients with high cholesterol levels.

The strength of the rotator cuff muscles largely depends on the tendons of these muscles. There are three main theories that describe the pathology of tendons: the vascular theory, the mechanical theory, and the neurological theory.[9] The vascular theory explains that tendons lack direct vascular supply, which can lead to tendon rupture and degeneration.[13] The mechanical theory suggests that the tendon's inability to respond to load can cause damage and degeneration. The neurological theory emphasizes the pro-inflammatory aspect of tendon degeneration. Hyperlipidemia can affect all three tendon health models. According to the vascular theory, individuals with hyperlipidemia are at an increased risk of atherosclerotic cardiovascular disease and have higher levels of plasma LDL components that can accumulate in tendons in the form of xanthomas.[9] This accumulation of LDL is directly linked to the neural theory of tendon degeneration as it contributes to the development of atherosclerosis, which includes inflammatory and immunological processes.[14] Atherosclerosis directly increases inflammation by allowing the accumulation of lipids within the innermost layer of the endothelial wall. Here, lipids are engulfed by macrophages to form "foam cells," and this accumulation of cholesterol within the foam cells causes subsequent mitochondrial dysfunction, cell death, and ultimately necrosis of the underlying tissue.[14] Finally, hyperlipidemia also affects the mechanical theory of tendon pathology. Hyperlipidemia-induced osteoclast migration in the humeral head, accompanied by bone mineralization and decreased tendon insertion strength at the infraspinatus attachment, ultimately affects the mechanical ability of the rotator cuff in response to load.

LIPID-LOWERING THERAPY: STATINS

Statins are a widely used class of drugs that lower LDL-C levels by inhibiting the enzyme HMG-CoA reductase, which is involved in cholesterol synthesis. By reducing cholesterol production in the liver, the amount of cholesterol in the bloodstream is decreased. This also leads to an increase in the expression of LDL receptors on the

surface of liver cells, allowing for more cholesterol to be removed from the blood. Numerous clinical studies have demonstrated the effectiveness of statins in improving lipid metabolism and preventing cardiovascular disease.[15] High doses of potent statins can effectively lower LDL-C levels by up to 50%, which can have a beneficial effect on the volume and stability of atherosclerotic plaques.

Different types of statins have varying abilities to lower LDL-C levels, with some being more effective than others. For example, at a dose of simvastatin 20–40 mg, LDL-C levels can be reduced by up to 35%–41%, while pravastatin 40 mg can reduce the levels by up to 34%.[16] Additionally, atorvastatin 20 mg or simvastatin 40 mg can reduce the levels by up to 40%.[16-18] At a higher dose of atorvastatin 80 mg or rosuvastatin 20 mg, LDL-C levels can be reduced by up to 54%.[16,19] The maximum reduction of approximately 60% was observed with rosuvastatin 40 mg.[19] However, doubling the statin dose only results in a further 6% reduction in LDL-C levels. While the rate of decrease in LDL-C levels is similar for patients with high and low starting levels, the absolute reduction is greater for those with higher starting levels.[20] Statins are also effective in reducing non-high-density lipoprotein cholesterol and triglyceride levels, although the rate of decrease in triglycerides depends on the baseline level.[21] However, the ability of statins to lower triglycerides is associated with reduced LDL-C levels.

STATINS IN RCT HEALING

Dolkart et al.[22] compared the in vivo and in vitro effects of atorvastatin on rotator cuff healing in a rat model of rotator cuff repair with a cyclooxygenase-2 (COX-2) inhibitor. In their study, they found that atorvastatin enhances tendon healing by stimulating tendon cell proliferation, migration, and adhesion through increased COX-2 activity and autocrine/paracrine prostaglandin E2 (PGE2) signaling. They also reported that this effect is mediated by prostaglandin E receptor 4 (EP4) signaling and that atorvastatin may play a positive role in tendon healing during the acute inflammatory phase after surgical tendon repair. Deren et al.[23] reported that simvastatin enhances muscle fiber force generation and prevents fibrosis and fat accumulation in a rat model of RCTs. In their results, in the experimental group treated with simvastatin, muscle fiber size was not affected, but muscle fiber-specific force increased by 20%. It also suggested that fibrosis after RCTs could be reduced through downregulation of type 1 collagen production, a marker of fibrosis. Between 5% and 10% of patients taking statins develop myopathy, and a minority of these patients progress to overt rhabdomyolysis. They thought that these conditions in their study were caused by a decrease in cholesterol levels because a significant decrease in cholesterol levels could destabilize the muscle fiber plasma membrane. In this context, they expected a potential upregulation of atrogin-1 by simvastatin, but found no difference.[23] Tucker et al.[24] evaluated the mechanical and histological properties of simvastatin-induced supraspinatus tendon in an animal model of diet-induced hypercholesterolemia. They fed the mice a high-cholesterol diet and induced hypercholesterolemic mice. They hypothesized that hypercholesterolemic rats treated with simvastatin would have improved tendon biomechanical and histological properties compared to hypercholesterolemic rats not receiving daily statin treatment. In the results, the biomechanical analysis showed an 18% increase in the cross-sectional area of the implantation area in the simvastatin-treated group (which is often associated with tendon fibrosis in response to injury, leading to poor mechanical parameters), and histological analysis showed that the simvastatin-treated group had significantly more spindle-shaped cells in the intermediate substance area compared to the control group. The use of simvastatin in patients with hypercholesterolemia does not appear to have a strong negative effect on the mechanical and histological properties of the tendon.[25] Hao et al.[26] noting in a previous report that simvastatin can activate vascular endothelial growth factor (VEGF) expression in osteoblasts through the phosphoinositide 3-kinase (PI3K) signaling pathway, evaluated the improvement of the healing of chronic rotator cuff injuries in a silk fibroin membrane containing simvastatin. They showed that simvastatin can activate VEGF expression in osteoblasts through the PI3K signaling pathway in a previous report and evaluated the improvement of chronic rotator cuff injury healing of silk fibroin membrane containing simvastatin. Simvastatin factor-loaded silk fibroin promotes proliferation and differentiation of bone marrow stem cells through beta-catenin signaling and, in particular, promotes tendon-bone healing, increases collagen formation, and shows better biomechanics than simvastatin alone.[26] According to these results, it is thought that statins may have a better prognosis in tendon healing when combined with other growth factors or appropriate scaffolds (Table 1).

There have been limited clinical studies investigating the efficacy of statins for the treatment of rotator cuff disease. However, a large population-based study conducted by Lin et al.[27] using the National Health Insurance Research Database found that statin use was associated with a reduced risk of rotator cuff disease compared to untreat-

Table 1. Effects of Statins on Rotator Cuff Treatment

Study	Level of evidence	Type of statin	Drug dose	Primary result
Amit et al. (2021)[28]	Prospective cohort design; human	Statin	Current National Institute for Health and Care Excellence guidelines*	Patient-reported outcomes, rotator cuff retear rate, and fatty infiltration on MRI at 12 months after rotator cuff repair in patients with hyperlipidemia treated with statins are similar to those in a control group
Hao et al. (2021)[26]	Comparison study; rat	Simvastatin	1 mg/mL	Simvastatin factor-loaded silk fibroin promotes the osteogenic differentiation of bone marrow stem cells through β-catenin signaling
Zeng et al. (2020)[15]	Cohort study; level III; human	Statin	The guidelines of the American College of Cardiology and the American Heart Association†	Patients with dyslipidemia with perioperative statin usage did not have poorer postoperative outcomes when compared with patients without dyslipidemia at 24 months.
Cancienne et al. (2017)[29]	Cohort study; level III; human	Atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin	National Drug Codes‡	The use of statin agents appeared to mitigate the need for revision rotator cuff repair.
Garcia et al. (2017)[13]	Retrospective cohort design; level III; human	atorvastatin, simvastatin, rosuvastatin, and lovastatin	Equivalent doses§	Hyperlipidemia was a significant risk factor for retears after arthroscopic rotator cuff repair. However, type and dosage of statin medication did not significantly affect the incidence of retear.
Deren et al. (2017)[23]	Basic science; *in vivo* animal study; rat	Simvastatin	25 mg/kg/day	Simvastatin, administered locally or systemically in a rat rotator cuff repair model, made no significant difference in maximum load to failure or histologic findings.
Tucker et al. (2016)[24]	Level II; prospective cohort design; treatment study; rat	Simvastatin	20 mg/kg/day	Insertion region cross-sectional area was significantly increased (18%) in the high-cholesterol-diet + simvastatin group compared to the high-cholesterol-diet group. Histological analysis showed the high-cholesterol-diet + simvastatin group had cells which were significantly more spindle shaped in the mid-substance region compared to the high-cholesterol-diet group.
Davis et al. (2015)[30]	Basic science; *in vivo* animal study; rat	Simvastatin	20 mg/kg/day	Simvastatin partially protected muscles against the loss in active force production that occurs after rotator cuff tear and dramatically reduced fibrosis as well.
Dolkart et al. (2014)[22]	Controlled laboratory study; rat	Atorvastatin	20 mg/kg/day	Atorvastatin enhances tendon healing by stimulating tenocyte proliferation, migration, and adhesion via increased COX-2 activity and autocrine/paracrine PGE2 signaling.

MRI: magnetic resonance imaging, COX-2: cyclooxygenase-2, PGE2: prostaglandin E2.
*All patients receiving statins (statin group) were prescribed these in the primary care setting prior to surgical repair for the treatment of hyperlipidemia, based on current National Institute for Health and Care Excellence guidelines. †A statin dose intensity and equivalency chart was employed for standardization per the guidelines of the American College of Cardiology and the American Heart Association. ‡Prescriptions for statins were identified in the database using National Drug Codes. §Statin medications were converted to their equivalent doses to determine whether the dosage of the medication had any effect on clinical outcomes.

ed hyperlipidemia patients. This association is believed to occur due to the anti-inflammatory role of statins in tendinopathy tissue, where they decrease the production of pro-inflammatory compounds such as isoprenoids and matrix metalloproteinases 3 and 9.[27] The study compared statin users with non-statin users for various types of rotator cuff disease, including calcific tendinitis, biceps tendonitis, bursitis, partial RCT, rotator cuff tendon sprains and strains, and full thickness RCTs.[28] The results showed a hazard ratio ranging from 0.44 to 0.71, indicating a significant reduction in the risk of rotator cuff disease with statin use ($p < 0.001$).[27] In another clinical study, Cancienne et al.[29] investigated the association between perioperative lipid levels (total cholesterol, LDL, and triglycerides) and revision surgery rates in 30,638 patients undergoing arthroscopic rotator cuff repair from a national insurance database. They found in a full-thickness RCT that patients with hyperlipidemia after arthroscopic rotator cuff repair had a higher reoperation rate than those without hyperlipidemia (odds ratio, 1.59; 95% confidence interval [CI],

1.17–2.16; $p = 0.020$). However, the revision rate of hyperlipidemic patients treated with statins was similar to that of normal subjects (odds ratio, 0.91; 95% CI, 0.69–1.20; $p = 0.501$). This suggests that even in the setting of persistent hyperlipidemia, perioperative statin use may reduce the risk of subsequent rotator cuff revision surgery equivalent to that of patients with normal lipid levels.[29]

In general, statins have been shown to be well tolerated by the majority of patients in large, high-quality randomized trials. However, there are potential side effects associated with statin therapy, and many patients are now receiving long-term treatment with these medications. The most common side effect related to statin use is statin-related myopathy.[31] A data analysis was conducted using the U.K. primary care database, which examined 15 years of prescription and diagnosis information for 77,240 statin users. Among the 4,258 cases of statin myopathy, with or without elevated creatinine kinase levels, it was found that 78.4% of these cases occurred either at the initiation of statin therapy or within 3 months of a dose increase. Additionally, 15.6% of the statin users experienced myopathy within 6 months of starting or changing the dose, while 6% of cases were diagnosed within 2 years after exposure to statins.[31] Furthermore, an analysis of the U.S. Food and Drug Administration (FDA) database revealed that out of 7,042 cases of statin-related rhabdomyolysis, 44.4% occurred within 1 month of starting statin therapy, and approximately 90% of cases occurred within 32 months of initiating statin therapy.[32] These findings support the idea that while most myopathy symptoms occur shortly after starting statin treatment, there is a possibility for symptoms to manifest years later.

SAFETY CONSIDERATIONS: HIGH-DOSE STATIN

While statins are generally considered safe and well-tolerated, they can cause skeletal muscle side effects that range from mild muscle pain to severe muscle breakdown (rhabdomyolysis). These side effects may limit the use of statins in a significant number of patients. According to a study involving over 10,000 current and former statin users, 25% of current users and 65% of former users reported experiencing muscle side effects. Additionally, almost two-thirds of former users stopped taking statins due to these side effects.[33] The European Society of Cardiology and the European Atherosclerosis Society guidelines for the treatment of hyperlipidemia recommend starting lipid-lowering medications with the aim of reducing LDL cholesterol to less than 55 mg/dL in patients who are at high risk of cardiovascular disease.[34] High-dose statins are often prescribed to achieve this goal, but they are also associated with an increased risk of myopathy, which is a muscle-related side effect.[18]

In June 2011, the FDA released a memo warning of an increased risk of muscle damage in patients taking the highest approved dose of simvastatin, which is 80 mg.[35] The Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial found that more patients in the simvastatin 80 mg group developed myopathy compared to those in the simvastatin 20 mg group.[36] Specifically, 52 cases of myopathy (0.9%) were reported in the simvastatin 80mg group, while only 1 case (0.02%) was reported in the simvastatin 20 mg group.[36] In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, it was found that the group receiving 80 mg of atorvastatin daily had a higher increase in liver enzyme levels compared to the group receiving 40 mg of pravastatin daily.[37] In the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) study, there were significantly more cases of elevated liver enzyme levels, occurring more than four times the normal limit, with three cases being diagnosed as hepatitis.[25]

The clinical studies suggest that statin therapy can potentially cause myopathy and tendon complications, and this effect may depend on the dose and the type of statin used. Retrospective studies indicate that rosuvastatin and atorvastatin are more likely to cause tendon-related side effects compared to other statins,[38] while simvastatin has mixed results.[27] Animal models have also shown that statin treatment can have negative effects on the mechanical properties and biochemical changes in the Achilles tendon.[39] However, when given during tendon or ligament healing, statins have been shown to improve tendon-bone healing and have a positive effect on cell migration and anti-fibrotic effects.[22] Furthermore, statins may have a positive effect on fibrosis of muscle tissue in the shoulder with an RCT.

CONCLUSION

Hyperlipidemia, or high cholesterol levels, is a risk factor for RCTs, and patients with hyperlipidemia have a higher risk compared to the general population. Statins, which are commonly used to lower cholesterol levels, may have implications for tendon healing in the context of hyperlipidemia, considering the vascular, mechanistic, and neurological theories of tendon pathology.[9] Animal studies have shown that atorvastatin can enhance rotator cuff tendon healing by activating COX-2 and increasing PGE2, which

stimulate tendon cell proliferation, migration, and adhesion.[22] Similarly, simvastatin can enhance muscle fiber force production and prevent fibrosis and fat accumulation in RCTs.[30] Clinical studies have shown that the use of statins reduced the risk of rotator cuff disease compared to patients with hyperlipidemia who did not use statins.[2] Additionally, hyperlipidemia patients who used statins after rotator cuff repair had a lower reoperation rate compared to those who did not use statins.[29] However, statin therapy can potentially cause myopathy and tendon complications,[40] and the risk may vary depending on the dose and type of statin used.[18,39] High-dose statins used to achieve very low LDL-C target levels may increase the risk of these complications. Indeed, the effects of statins on tendon healing after RCTs are still a subject of controversy. While there are studies suggesting positive effects of statins on tendon healing, there are also potential risks associated with their use. Furthermore, the molecular mechanism underlying the impact of high-intensity statin therapy aimed at achieving more aggressive lipid-lowering targets on rotator cuff healing requires further investigation.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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