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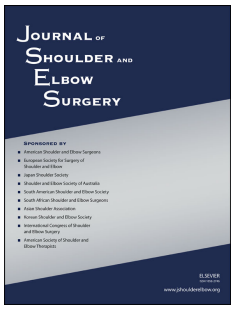

Does statin-treated hyperlipidemia affect rotator cuff healing or muscle fatty infiltration after rotator cuff repair?

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Does statin-treated hyperlipidemia affect rotator cuff healing or muscle fatty infiltration after rotator cuff repair?

Running title: Effect of statin-treated hyperlipidemia on rotator cuff repair

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Title of the study:

Does statin-treated hyperlipidemia affect rotator cuff healing or muscle fatty infiltration after rotator cuff repair?

Abstract

Purpose: Hyperlipidemia is linked to poor tendon to bone healing and progression of fatty infiltration after rotator cuff repair. Statins effectively treat hyperlipidemia, but it is unknown if they have any potential detrimental effects following rotator cuff repair. The aim of this study was to evaluate the effect of statins on rotator cuff healing and fatty infiltration following repair.

Methods: A total of 77 patients undergoing arthroscopic rotator cuff repair were recruited prospectively, 38 patients who were prescribed a statin (statin group) for hyperlipidemia and 39 patients not on statin (control group). The patients who did not have both preoperative and one-year postoperative MRI scan were excluded from the study. Patient reported outcome measures, namely the Western Ontario Rotator Cuff index, Constant-Murley score, American Shoulder and Elbow Surgeons score, and Disability of Arm, Shoulder and Hand score were collected preoperatively and at one year. Fatty infiltration was assessed on MRI according to the Goutallier grading preoperatively and at 12 months, rotator cuff healing was assessed at 12 months according to the Sugaya classification. Following propensity score weighting to adjust for baseline imbalances, twelve-month outcomes were compared between the two groups.

Results: At 12 months, all patient reported outcome measures had improved significantly compared to baseline (WORC, 85.9 vs 32.5, $p<0.001$; ASES, 87.3 vs 37.5, $p<0.001$; Constant, 77 vs 31, $p<0.001$; DASH, 13.6 vs 61.4, $p<0.001$). There was no significant difference in postoperative scores between the two groups (WORC, 84.9 vs 89.6, $p=0.94$; ASES 87.5 vs 86.6, $p=0.40$; Constant, 77 vs 81, $p=0.90$; DASH, 14.4 vs 11.4, $p=0.14$, statin vs control respectively), and in three of these the 95%CIs excluded a clinically meaningful difference. Similarly, rotator cuff healing at 12 months and Goutallier fatty infiltration grades were comparable between the two groups. Retear was seen in six (15.8%) patients in the

statin group and eight (20.5%) patients in the control group. Progression of fatty infiltration was seen in four (10.5%) patients in the statin and four (10.3%) in the control group. Statin use did not demonstrate significant association with either retear risk (P = 0.41) or progression of fatty atrophy (P = 0.69).

Conclusion: Patient-reported outcomes, rotator cuff retear rate and fatty infiltration on MRI at 12 months post rotator cuff repair in patients with hyperlipidemia treated with statins are similar to a control group.

Level of evidence: Level II; Prospective Cohort Design; Treatment Study

Keywords: Fatty infiltration; hyperlipidemia; re-tear; rotator cuff repair; statin

Degenerative rotator cuff tears are prevalent in up to 65% of individuals over age 70 years.[35] The repair process is inherently flawed, with structurally weaker type III collagen at the repair site which commonly results in subsequent re-tear. Degenerative tears are commonly associated with fibrosis and fatty infiltration of the rotator cuff muscles.[6] The amount of fatty infiltration, as measured with the Goutallier classification,[18] is predictive of poor functional outcome post repair.[24]

Hyperlipidemia is a recognized risk factor for degenerative rotator cuff tear[1,27] and fatty infiltration of rotator cuff muscles.[30] Deposition of lipid as oxidized low-density lipoprotein forms tendon xanthoma,[24] resulting in altered mechanical properties, chronic inflammation, and impaired circulation, contributing to the pathogenesis of rotator cuff tear and subsequent poor tendon-bone healing after repair.[5,9,28,40] In animal models replicating hyperlipidemia, a greater incidence of poor healing or retear[5,10,14,28] has been reported along with progression of fatty infiltration of the rotator cuff muscles following surgical repair.[10] Likewise, a large population based study has shown higher rate of revision rotator cuff repair in patients with hyperlipidemia.[8]

Statins are commonly prescribed cholesterol-lowering medication in hyperlipidemia. They reduce hepatic cholesterol synthesis by inhibiting hydroxy-methyl-glutaryl coenzyme A

(HMG-CoA) reductase in the mevalonate pathway. Approximately 10-15% of statin users suffer specific side effects affecting the muscle and tendon.[2] The more common side effects are tendinopathy and tendon ruptures (mostly in tendoachilles and biceps tendon).[3,29] At the cellular level, statins lead to increased release of collagenases (matrix metalloproteinases 1 and 13) by tendon fibroblasts which are believed to cause disruption of extracellular matrix in the tendons resulting in tendinopathy.[15] At supratherapeutic levels, statin causes imbalance in extracellular matrix components affecting muscle cell viability resulting in more drastic consequences as myopathy and rhabdomyolysis.[2,12,26]

With regards to rotator cuff tear, statins have shown some beneficial effects.[7,11,27] Dolkart et al[14] studied 48 healthy (non-hyperlipidemic) rats and found enhanced biomechanical properties (maximal load to repair failure and stiffness) of repaired cuff tendon in statin-treated rats compared to saline-treated rats ($P < 0.001$). In contrast, Deren et al,[13] in their study of 80 healthy (non-hyperlipidemic) rats, found similar strength (maximum load to repair failure) and histology (collagen organization, cellularity, vascularity, cartilage formation, new bony matrix deposition) at the tendon-bone healing site in rats treated with local or systemic statin versus non-treated rats ($P > 0.05$). The results of these contradictory studies make it difficult to draw firm conclusions regarding the effect of statin. Moreover, these animal studies did not study the effect of statin use in a hyperlipidemic environment which is usually the clinical scenario, representing a fundamental the animal model.

There are few clinical studies which have investigated the effects of statins in rotator cuff disease. A large population-based study by Lin et al[27] studied over a million patients using the National Health Insurance Research Database and demonstrated a reduced risk of rotator cuff disease compared to untreated hyperlipidemic patients. This association is believed to occur because of statin's anti-inflammatory role in tendinopathic tissues, where it reduces the formation of pro-inflammatory compounds such as isoprenoids and matrix metalloproteinase 3 and 9.[7] Statin use correlated with a reduced risk of rotator cuff disease (including calcific tendinitis, biceps tenosynovitis, bursitis, partial rotator cuff tear, sprains and strains of rotator cuff tendon along with full thickness rotator cuff tear) compared to non-statin use (HR 0.44-0.71, $P < 0.001$).[27]

Thus far, statins role in re-tear and fatty infiltration following rotator cuff repair has not been studied in a clinical trial setting. Therefore, this study was undertaken with the aim to evaluate the effect of hyperlipidemia treated by oral statin on re-tear rate and fatty infiltration

as assessed by magnetic resonance imaging (MRI) and functional outcomes 12 months post repair.

Materials and methods

This was a prospective study carried out at a single institution, investigating isolated postero-superior rotator cuff tears over a period of five years from February 2010 to December 2015 (IRB approval: IRAS 27416). All patients undergoing arthroscopic repair of isolated postero-superior full-thickness rotator cuff tear, after failed conservative treatment were recruited to the study in a continuous manner. The strict inclusion criteria was the availability of both pre and 12 months postoperative MRI. The exclusion criteria were patients with partial tear, subscapularis tear, previous shoulder surgery, irreparable tears, rotator cuff tear arthropathy or osteoarthritis, proximal humerus fracture on the operated shoulder and ongoing insurance/compensation claim related to the index shoulder.

The patient records including drug charts, general practitioner referral letter and preoperative anesthetic charts, were reviewed. Patients were divided into two groups dependent on whether they were prescribed oral statins. All patients on statins (statin group) were prescribed them in the primary care setting prior to surgical repair for the treatment of hyperlipidemia, based on current National Institute for Health and Care Excellence (NICE) guidelines.[31] The control group consisted of patients not on statins.

The surgery was performed by four fellowship-trained surgeons. Following diagnostic arthroscopy, the size of the rotator cuff tear was recorded and then repaired using a technique (single row or double row or suture-bridge repair) based on the discretion of the operating surgeon. Any concomitant pathologies, such as, long head of biceps tendon pathology, subacromial impingement and acromioclavicular arthritis, were addressed as necessary. Postoperatively, all patients underwent uniform rehabilitation as per established departmental protocols, which included six weeks of immobilization, with strengthening commencing at 3 months.

All patients had MRI scan using a 3 Tesla, Magnetom Trio scanner (Siemens, Erlangen, Germany). MRI was performed within three months prior to surgery and then repeated at one

year following repair. The MRI was assessed by two musculoskeletal trained radiologist for fatty infiltration of the rotator cuff muscles using Goutallier grade[18] and rotator cuff healing at the tendon-bone interface as per the Sugaya classification.[36] Sugaya grade 4 (minor discontinuity as small full thickness tear) and 5 (major discontinuity as medium to large full thickness tear) were considered as failure of tendon healing and re-tear. Progression of fatty infiltration was noted if there was progression of Goutallier grade following repair.

Functional outcome of all patients was assessed using the Western Ontario Rotator Cuff (WORC) index, Constant-Murley score, American Shoulder and Elbow Surgeons (ASES) score, and Disability of arm, shoulder and hand (DASH) score, both at baseline and at one year post repair. The minimum clinically important difference (MCID) of each score was: WORC 15,[16] Constant-Murley 10.4,[25] ASES 15.5,[22] and DASH 16.3.[38] The surgeons performing the surgery, outcome assessors and the radiologist were blinded to the patient's groups.

Statistical analysis

The distribution of continuous variables was assessed using QQ-plots and non-parametric methods were used where appropriate. The baseline characteristics of the two groups were compared using two-tailed t-tests for continuous variables and chi-square/Fisher Exact test for categorical variables. The standardized mean difference (SMD) was determined for each baseline variable (covariate), and any difference above 10% was considered to indicate a meaningful imbalance.[4] If the imbalance was above 10%, propensity score matching using a covariate balancing approach[20] was used to compare the 12-months patient-reported and MRI outcomes. The adjusted baseline covariate balance and the adjusted difference in 12-month outcomes between the two groups were estimated using inverse probability treatment weighting (IPTW), where the inverse of the propensity scores was used as sampling weights.[4] An SMD between the covariates above 10% for the weighted samples was assumed to indicate a meaningful remaining covariate imbalance and handled as described below.[4,32]

The improvement in patient reported outcomes post-surgery for the entire patient population was analyzed using Wilcoxon signed rank tests. Between the two groups, the continuous outcomes were compared using weighted quantile regression models, binary outcomes compared using weighted Poisson regression and ordinal outcomes compared using weighted proportional odds models. All covariates with an imbalance above 10% in the

weighted samples were included in these analyses as covariates, an approach known as "doubly robust".[16] The Goutallier classification of fatty infiltration might have a higher value in hyperlipidemia patients, even after statin treatment, and could therefore correlate with statin treatment. If a covariate correlates better with treatment than with outcome, its inclusion in the analysis could introduce bias.[4] We therefore also performed a sensitivity analysis by omitting the Goutallier classification as a covariate and repeating the re-tear risk calculation. The results of the proportional odds model were reported as the probability of ordinal superiority (POS), the chance that a patient in the treatment group has a higher ordinal score than a patient in the control group. In all analyses, robust "sandwich" estimators of variance were used.[4] A two-sided p-value below 0.05 was assumed to denote statistical significance. The differences in patient-reported outcomes between the two groups was interpreted by comparing their 95% confidence intervals (95%CIs) to their MCID. If the MCID fell outside the 95%CI, the difference was deemed not important. All statistical analyses were performed using R vs 4.0.2 and the packages CBPS, cobalt, lstest and rms.

Results

A total of 89 eligible patients were recruited; 12 patients were excluded due to unavailability of postoperative MRI. A total of 77 patients formed the final study group of which 38 used statins. None of the patients were lost to follow-up. The group demographics and other preoperative parameters are shown in Table 1. The two groups were poorly balanced for all but two baseline variables (ASES and Constant score), with imbalances up to 62% of their SD (Fig 1). All imbalances apart from the WORC index were adequately corrected by using inverse propensity score weighting (Fig 1). Since the remaining imbalance of 13% in the baseline WORC score was above 10%, this score was used as a covariate in all further analyses. The effective sample sizes of the two weighted samples were calculated as 38 for the statin group and 26 for the control group.

Additional procedures were performed in both groups with no significant difference: biceps tenotomy (15 in statin, 17 in control); biceps tenodesis (six in statin, eight in control);

subacromial decompression (25 in statin, 23 in control); acromio-clavicular joint excision (three in statin, two in control group) ($P > 0.05$).

The postoperative MRI demonstrated an overall re-tear rate (Sugaya grade 4 and 5) of 14/77 (18%, 95%CI 11-28%). There were six (15.8%) re-tears in the statin and eight (20.5%) in the control group (Fig 2), with no evidence for a difference in re-tear risk between the groups (RR=0.65, 95%CI 0.24-1.8, $P = 0.41$) (Table 2). This was reflected in the comparison of Sugaya grades, which suggested that the balance of probabilities was tilted favorably towards the statin group with patients using statins having a 38% chance (95%CI 28-52) to have worse repair integrity, or in other words 62% chance to have better repair integrity than patients not using statins (Table 2).

There was no significant difference in postoperative fatty infiltration between the two groups ($P = 0.24$) (Table 2). None of the patients in either group had reversal of fatty infiltration. However, progression of fatty infiltration following surgery was seen in four (10.5%) patients in the statin and four (10.3%) patients in the control group. No evidence was found for a significant difference between the two groups ($P = 0.52$) (Fig 3).

The preoperative Goutallier classification showed a large imbalance between the two groups, indicating it correlated well with treatment (Table 1). On repeating the propensity score analysis while excluding the Goutallier classification, the remaining imbalances were similar to those found in the full analysis, with only the WORC more than 10% out of balance. However, the imbalance in the Goutallier classification remained high post repair. The relative re-tear risk calculated in this way was close to that from the full analysis (0.78, 95%CI 0.28-2.20), as was the probability of a higher Sugaya grade (42%, 95%CI 28-56%).

None of the four postoperative patient-reported outcomes were distributed normally. Compared to baseline, all patient-reported outcomes improved significantly when analyzed for the whole group (Table 3). For each score, the lower 95% confidence levels of the difference in medians was at least twice the MCID, suggesting a clinically meaningful improvement for all scores. No evidence was found for a difference in postoperative patient-reported outcomes between the two groups (Table 2). The 95% confidence interval of the differences in outcome excluded the MCID for two scores (ASES and DASH) and was very close to the MCID for one (Constant). Only for the WORC index, a clinically important difference between the two groups could not be excluded.

Discussion

This is the first prospective clinical study to evaluate the effect of hyperlipidemia treated by oral statin on re-tear rate, fatty infiltration and clinical outcome following rotator cuff repair. The most important finding of this study is that hyperlipidemia treated by oral statin is unlikely to adversely affect the integrity of the repair or the clinical outcome following rotator cuff repair. Moreover, it was found that if statin use would influence the patient-reported outcomes, its influence is likely to be below the MCID on three of the four scores which were investigated. If statin use would influence repair integrity, then most likely the effect as measured by Sugaya grade is beneficial.

MRI at 12 months revealed similar re-tear rates in the statin-treated hyperlipidemia group versus a non-statin non-hyperlipidemia control group. The results contradict the study of Garcia et al[17] who evaluated 86 rotator cuff repairs with ultrasound (US) at six months post-surgery. They found significantly high odds of partial and full thickness re-tear in statin-treated hyperlipidemia patients (45.5%) in comparison to non-hyperlipidemia patients (11.3%) [OR 6.5, $P < 0.001$]. The difference in re-tear risk between this study cannot be explained by the different diagnostic techniques (US versus MRI), which have comparable diagnostic accuracy.[34] More likely explanations are the nature of the studies or the influence of confounding factors. Garcia et al[17] was a retrospective study involving a subpopulation of 85 out of 401 (21%) rotator cuff repair patients who had postoperative ultrasound, a sampling method that may have led to selection bias. Our prospective study on the other hand involved a planned postoperative MRI, and therefore included a large proportion (77/89 or 87%) of our patients, reducing the risk of selection bias. With respect to confounding factors, Garcia et al[17] did not attempt to account for them by balancing the two groups or by including known confounders as covariates in their analyses. Instead, it reported that none of six potential confounders had a statistically significant influence on re-tear rates, implying that this would justify a direct comparison between the two study groups. However, statistical significance is a poor criterion when deciding whether adjusting for confounders is needed.[21] Our study used propensity score weighting to balance the two groups for all measured confounders, increasing the probability that we assessed the true effect of statin-treated hyperlipidemia. An unaddressed confounder by Garcia et al[17] is the time between surgery and imaging follow-up. The mean time to follow-up was 7 months, with a range of 4-9 months. However, the critical period for re-tear extends to 6 months,[33] suggesting the scans prior to six months

may have introduced error. Unfortunately, no information on the timing of scanning in the two groups was provided and therefore its potential effect cannot be assessed. In our prospective study, all MRI scans were performed at 12 months postoperatively, ensuring it would capture almost all re-tears.

Cancienne et al[8] reported outcomes of 30,638 patients following rotator cuff repair using an insurance-based database of patient records. They found increased revision surgery rates in patients with hyperlipidemia than in patients without hyperlipidemia (OR 1.59, 95%CI 1.17-2.16, P = 0.020). However, the revision rate in hyperlipidemic patients treated with statins was very similar to that in healthy patients (OR 0.91, 95%CI 0.69-1.20, P = 0.501). Although rotator cuff re-tears have an adverse effect on clinical outcome,[39] they can be largely asymptomatic and therefore do not necessarily require surgery.[23,33] The revision rates reported therefore might still hide a difference in re-tear rates given no post-surgical imaging was performed. The results from the current study would suggest this is not the case.

Following surgery, patients in both groups reported a significant and clinically important improvement in all four patient reported scores, with a magnitude of at least twice the minimum clinically important difference (MCID) based on the lower 95% confidence limits. The clinical outcomes post-surgery were comparable between the two groups, with 95% confidence intervals or "plausible ranges" suggesting that this study excludes any differences larger than the MCID for three of the four outcomes. Our finding of equivalent functional outcomes matches the findings from a recent retrospective study by Zeng et al[41] investigating the outcome of rotator cuff repair in 266 patients with hyperlipidemia treated with statins. They also found no evidence for a difference in functional outcome up to 24 months after surgery, and suggested that a well-designed prospective studies focused on concurrently assessing clinical and radiological postoperative outcomes would be useful to validate their finding. The results of this study do indeed substantiate their findings and that there is no detrimental effect of statin-treated hyperlipidemia on clinical outcome.

Finally, we assessed the effect of statin-controlled hyperlipidemia on fatty infiltration. At baseline, we found no significant difference between the two groups in fatty infiltration levels as assessed by the Goutallier classification, but this classification did show the largest imbalance between the two groups among all baseline variables. Hence, although statin might reduce hyperlipidemia-induced fatty infiltration, some difference with our control group probably remained. Following repair, similar levels and similar progression of fatty

infiltration between the two groups was found. The effect of hyperlipidemia on fatty infiltration after administrating statins has so far only been investigated in animal models. Davis et al[11] induced a rotator cuff tear in healthy (non-hyperlipidemic) rats and measured lipid content in rotator cuff muscle four weeks later. They found similar total triglyceride levels between statin treated and non-treated rats, and concluded that statin does not prevent fatty infiltration in a normal lipid environment. Conversely, Chung et al[10] reported progression of fatty infiltration after rotator cuff repair in rabbits who were exposed to persistent hyperlipidemia, however statin treatment led to lower fat-to-muscle proportion and better tendon-to-bone interface with less fat interposition compared to rabbits on high cholesterol diet without statin. This supported the protective role of statin against fatty infiltration in the presence of hyperlipidemia. Taken together, the results of the present study and the animal studies suggest that statin treatment of hyperlipidemia has a potential role in preventing further fatty infiltration of the repaired rotator cuff.

The amount of fatty infiltration might be higher in hyperlipidemia patients, despite being treated with statins, and therefore correlates with the group membership in our study. We did indeed find that the Goutallier classification showed the highest amount of imbalance among the covariates in our study despite similar tear size. Including such "instrumental variables" in the analysis might introduce bias.[4] However, excluding the Goutallier classification from our analyses gave only minor changes to the calculated re-tear risk and Sugaya score. This sensitivity analysis therefore indicates that the Goutallier classification did not bias our results.

This study is not without limitations. One limitation was a lack of untreated hyperlipidemic patients in our cohort, which could have served as an extra control group to compare with the two current groups. However, considering the higher re-tear risk and fatty infiltration levels in hyperlipidemia patients[10,28,30] and the secondary effects of hyperlipidemia on the cardiovascular system, there are ethical issues in trying to construct a positive control group. Secondly, serum lipid levels were not measured prior to the study. Including them in the analysis might have allowed to achieve a better balance between the groups, for instance by accounting for possible undiagnosed cases of hyperlipidemia in the control group or treatment failure in the statin group. We did not measure serum lipid because studying the effect of statins was the original objective of this cohort study. A full lipid profile is normally ordered by general practitioners before prescribing statins as part of the primary and

secondary prevention of cardiovascular diseases (CVD) in hyperlipidemia patients.[31] The primary prevention is undertaken in all patients over 40 years of age with altered lipid profile and more than 10% risk of developing CVD based on QRISK3 tool.[19] However, this data is not routinely collected before rotator cuff surgery. Thirdly, there is a possibility of performance bias in this study due to the different repair techniques used by different surgeons (single or double row or suture bridge repair).

A final limitation concerns the sample size in the current study. The sample size was based around a continuous outcome, namely the need to demonstrate a difference in functional outcome of at least the MCID. And indeed, the sample size was large enough to demonstrate that the differences in functional outcomes from statin-treated hyperlipidemia were highly likely smaller than the MCID. However, studies using binary outcomes such as re-tear risk require larger sample sizes.[37] Although we demonstrated that the relative re-tear risk in statin-treated hyperlipidemia patients is unlikely above 1.8 times that in control patients, surgeons might want more reassurance. However, even a study powered to demonstrate that the relative risk is unlikely to be more than 1.5 (or the odds ratio below 1.7) would already need 412 patients in each group. This calculation assumes a 5% alpha error rate, 80% power, and identical re-tear risks of 18% in both groups. Clearly, such a study would have to be multicentral and rely on strict MRI or ultrasound follow-up. Such larger studies could confirm our findings and narrow down our risk estimates. On the other hand, when using the full Sugaya grading system instead of its dichotomized version, the balance of probabilities indicated that statin-treated hyperlipidemia patients had a better repair integrity at 12 months. We consider this a finding worth of further investigation, and the required sample size would be much smaller than 824 patients.

Conclusion

The results support the role of statin in reversing the adverse effect of hyperlipidemia on the results of rotator cuff surgery. In this study, statin treatment in patients with hyperlipidemia patients reduced re-tear rates and progression of fatty infiltration to similar rates found in patient without hyperlipidemia, suggesting a positive influence of statin in hyperlipidemia patients who need rotator cuff repair. Moreover, statin-treated hyperlipidemia patients and

non-hyperlipidemia control patients had no clinically important difference in three of the four clinical outcomes we investigated.

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Figure Legends

Figure 1: Balance of baseline characteristics (covariates) in unadjusted and adjusted sample. The imbalance of each characteristic was characterized by its SMD (standardized mean difference). The two dashed vertical lines represent the 10% criterion denoting meaningful imbalance.

Figure 2: MRI T2 FS coronal image showing full-thickness tear in supraspinatus tendon (Sugaya grade 5) following repair in a patient in the statin group

Figure 3: MRI T1 sagittal image showing fatty infiltration in supraspinatus (A) Goutallier grade 1 before surgery; (B) Goutallier grade 2 after surgery for a patient in the statin group

Table Legends

Table 1: Demographic and baseline clinical characteristics

Table 2: Unadjusted ("raw") outcomes (12 months postoperative) for the two study groups and adjusted differences between them

Table 3: Overall patient-reported outcomes in the whole study population

Characteristics		Statin	Control	*P* value	SMD
N		38	39		
Age (years)		61.7 (6.6)	60.2 (7.4)	0.35	0.215
Sex	F	15 (39.5%)	20 (51.3%)	0.42	0.239
	M	23 (60.5%)	19 (48.7%)		
Tear size (mm)		23.2 (12.7)	21.0 (13.2)	0.47	0.167
Repair types	Single-row	7 (19.4)	12 (31.6)	0.49	0.281
	Double-row	8 (22.2)	7 (18.4)		
	Suture-Bridge	21 (58.3)	19 (50.0)		
Goutallier	0	5 (13.2%)	9 (23.1%)	0.064	0.616
	1	26 (68.4%)	28 (71.8%)		
	2	7 (18.4%)	1 (2.6%)		
	3	0 (0.0%)	1 (2.6%)		
	4	0	0		
Clinical outcome scores	WORC	29.7 (15.5)	35.8 (15.2)	0.087	0.395
	ASES	37.9 (20.0)	38.8 (16.3)	0.84	0.046
	Constant	33.3 (18.9)	34.7 (18.7)	0.76	0.071
	DASH	62.3 (15.0)	54.9 (18.7)	0.064	0.435

Notes: Continuous variables reported as means (SD), categorical variables reported as number (%). *P* values based on 2-tailed t-tests for continuous variables and chi-squared tests or Fisher's exact test (Goutallier) for categorical variables. WORC, Western Ontario Rotator Cuff index; ASES, American shoulder and elbow score; DASH, Disability of arm, shoulder and hand score; n, Number of patients; SMD, Standardised Mean Difference.

Outcome	Level	Statin	Control	Adjusted difference, RR or POS (95% CI)	*P* value
Cuff healing	Normal	32 (84.2)	31 (79.5)	0.65 (0.24 to 1.80)	0.41
	Re-tear	6 (15.8)	8 (20.5)		
Sugaya grade	1	17 (45.9)	12 (30.8)	0.38 (0.25-0.52)	0.098
	2	10 (27.0)	14 (35.9)		
	3	4 (10.8)	5 (12.8)		
	4	3 (8.1)	2 (5.1)		
	5	3 (8.1)	6 (15.4)		
Goutallier classification	0	4 (10.5)	7 (17.9)	0.59 (0.44-0.72)	0.24
	1	24 (63.2)	28 (71.8)		
	2	9 (23.7)	2 (5.1)		
	3	1 (2.6)	2 (5.1)		
	4	0	0		
Fatty infiltration	Same	34 (89.5)	35 (89.7)	1.59 (0.39-6.4)	0.52
	Progression	4 (10.5)	4 (10.3)		
WORC		84.9 (56.2-95.2)	89.6 (70.9-95.7)	-0.7 (-19.1 to 6.0)	0.94
ASES		87.5 (64.6-94.9)	86.6 (63.3-96.7)	-3.5 (-9.9 to 4.1)	0.40
Constant		77 (62-83.5)	81 (66.5-86.5)	-0.5 (-10.6 to 4.4)	0.90
DASH		14.4 (5.1-33.7)	11.4 (2.3-20.3)	8.1 (-0.6 to 12.9)	0.14

Notes: Categorical variables reported as number (%) and their differences as RR (relative risk) or POS (probability of ordinal superiority) (95%CI). Continuous outcomes (WORC, ASES, Constant, DASH) reported as medians (IQR) and their differences as medians (95%CI). Adjusted differences, 95%CI and *P* values based on weighted quantile regression models for continuous outcomes, weighted Poisson regression models for binary outcomes and weighted proportional odds models for ordered-categorical outcomes, with weights determined from inverse propensity scores. WORC, Western Ontario Rotator Cuff index; ASES, American shoulder and elbow score; DASH, Disability of arm, shoulder and hand score.

Outcome	Baseline		12 Months		Difference (95% CI)	*P* value	MCID
	Median (IQR)	Range	Median (IQR)	Range			
WORC	32.5 (20.1-42.9)	4.2-72.4	85.9 (62.4-95.4)	0-100	45.0 (38.1-51.8)	< 0.001	15
ASES	37.5 (24.3-50.8)	3.3-88.3	87.3 (64.2-96.6)	8.3-100	40.2 (32.6-48.0)	< 0.001	15.5
Constant	31 (20-49)	2-78	77 (65-85)	8-100	39.0 (33.0-44.8)	< 0.001	10.4
DASH	61.4 (47.5-70.4)	27.3-70.4	13.6 (4.5-27.3)	0-81.8	-39.3 (-44.8—34.0)	< 0.001	16.3

Notes: *P* values based on Wilcoxon signed-rank test. The 95%CIs of the difference in medians are non-parametric intervals. WORC, Western Ontario Rotator Cuff index; ASES, American shoulder and elbow score; DASH, Disability of arm, shoulder and hand score; MCID, Minimum Clinically Important Difference.