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SCIENTIFIC ARTICLE

Statin use and longitudinal changes in quantitative MRI-based biomarkers of thigh muscle quality: data from Osteoarthritis Initiative

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Abstract

Objective To assess whether changes in MRI-based measures of thigh muscle quality associated with statin use in participants with and without/at-risk of knee osteoarthritis.

Methods This retrospective cohort study used data from the Osteoarthritis Initiative study. Statin users and non-users were matched for relevant covariates using 1:1 propensity-score matching. Participants were further stratified according to baseline radiographic knee osteoarthritis status. We used a validated deep-learning method for thigh muscle MRI segmentation and calculation of muscle quality biomarkers at baseline, 2nd, and 4th visits. Mean difference and 95% confidence intervals (*CI*) in longitudinal 4-year measurements of muscle quality biomarkers, including cross-sectional area, intramuscular adipose tissue, contractile percent, and knee extensors and flexors maximum and specific contractile force (force/muscle area) were the outcomes of interest.

Results After matching, 3772 thighs of 1910 participants were included (1886 thighs of statin-users: 1886 of non-users; age: 62 ± 9 years (average ± standard deviation), range: 45–79; female/male: 1). During 4 years, statin use was associated with a slight decrease in muscle quality, indicated by decreased knee extension maximum (mean-difference, 95% *CI*: − 1.85 *N*/year, − 3.23 to − 0.47) and specific contractile force (− 0.04 *N*/cm^2/year, − 0.07 to − 0.01), decreased thigh muscle contractile percent (− 0.03%/year, − 0.06 to − 0.01), and increased thigh intramuscular adipose tissue (3.06 mm^2/year, 0.53 to 5.59). Stratified analyses showed decreased muscle quality only in participants without/at-risk of knee osteoarthritis but not those with established knee osteoarthritis.

Conclusions Statin use is associated with a slight decrease in MRI-based measures of thigh muscle quality over 4 years. However, considering statins' substantial cardiovascular benefits, these slight muscle changes may be relatively less important in overall patient care.

Keywords Statin · MRI · Muscle quality · Deep learning · Knee osteoarthritis

Introduction

Statins are 3-hydroxy-3-methyl-glutaryl coenzyme A or HMG-CoA reductase inhibitors and have been consistently among the three most frequently prescribed medications in the USA [1]. Statins are safe and have overwhelmingly documented benefits for protection against cardiovascular outcomes [2]. However, statins are known to have various effects on the musculoskeletal system, including well-documented subjective statin-associated musculoskeletal symptoms (SAMS) as one of their most common side effects. Conversely, potential protective effects on the musculoskeletal system have also been reported, such as a potential role in protecting against knee osteoarthritis (KOA) progression [3–5]. SAMS, including myalgia, are reported in up to one-third of the current [6] and up to two-thirds of former statin users [7]. However, while statin use is rarely associated with myositis, myonecrosis, rhabdomyolysis, and markedly elevated creatine kinase (CK) [8] levels, studies have shown that statin use commonly leads to a mild but statistically significant increase in serum CK, suggesting that statins produce mild muscle injury even among asymptomatic subjects in the absence of any change in muscle strength and function [9].

While slight asymptomatic increases in CK levels [8] and mild muscle symptoms are prevalent [10], to date, there has

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been no robust evidence on whether statin use is associated with worsening muscle quality in the absence of rare frank rhabdomyolysis. Detecting marked worsening of muscle quality and subsequent weakness in the lack of clinically overt rare incidences of myositis, myonecrosis, and rhabdomyolysis would raise a concern for the wide use of statin in clinical practice. This potential concern may be even more critical in a large subgroup of statin users with comorbidities directly affected by possible deterioration in muscle quality, such as knee osteoarthritis (KOA) [11, 12]. Prior works have demonstrated a close relationship between thigh muscle quality and KOA clinical outcome. Not only is KOA associated with changes in thigh muscle volume, composition, and force, but also such changes in thigh muscles can be predictive of cartilage loss, known as one of the primary biomarkers for KOA progression [11, 12].

In this study, we used a propensity-score (PS) matched design and 4-year longitudinal data from the Osteoarthritis Initiative (OAI) study. We aimed to investigate the association between statin use and changes in thigh muscles' quality using validated non-invasive magnetic resonance imaging (MRI) biomarkers such as cross-sectional area (CSA), contractile percentage, and specific contractile force [13–15], in OAI study participants with KOA and those without/at-risk of KOA at the baseline assessment.

Materials and methods

Data source and study sample

In this retrospective cohort study, we used data from the longitudinal multicenter OAI study (2004–2015 clinicaltrials.gov identifier: NCT00080171). The OAI comprises data on 4796 participants aged 45–79 years within three subcohorts, the Incidence group (participants with risk factors and at-risk of KOA; *N*: 3284), the Progression group (participants with existing KOA; *N*: 1390), and the non-exposed Control group (participants without KOA and its risk factors *N*: 122). Informed consent was obtained from all individual participants included in the study. Institutional review boards of four OAI collaborating centers have approved the OAI study's Health Insurance Portability and Accountability Act-compliant protocol [16]. The protocols for data collection are described in OAI "Operations Manuals" (https://nda.nih.gov/oai/study_documentation.html). The used datasets are presented in Supplemental Table 1. Participants with missing or unacceptable quality thigh MRIs in baseline, 2nd, or 4th-year follow-up visits were excluded (Exclusion #1, Fig. 1). Also, thighs of knees with missing baseline radiographic Kellgren-Lawrence (KL) grading (used to assess KOA status) were excluded (Exclusion #2, Fig. 1).

Exposure definition

Based on the OAI protocols, participants were asked to bring their medications at each baseline and annual follow-up visit and questioned about medication types, frequency, and duration of use. In this study, all the related data on the type of statin (including atorvastatin, lovastatin, fluvastatin, simvastatin, pravastatin, and rosuvastatin), and duration of statin use were extracted from the OAI medication inventory forms' (MIFs) dataset. Participants who reported statin use at baseline or either of four annual follow-up visits were categorized as statin users, and participants with no statin use before or during the cohort period were defined as non-users.

Baseline radiographic KOA assessment

Radiographic KOA was assessed using posteroanterior weight-bearing radiographs with a fixed-flexion (15°) protocol [16]. Knee radiographs were read at one OAI center and were scored with semi-quantitative KL grades with knees with KL grade ≥ 2 considered as with KOA [17].

Muscle contractile force determination

Participants completed isometric knee extension and flexion maximum voluntary contractions using the "Good Strength Chair" apparatus (Metitur, Jyväskylä, Finland) three times [18]. The highest force of the three measurements represented the maximum contractile force for each thigh (measured in newtons or *N*).

MRI acquisition and thigh MRI muscle segmentation

As mentioned in the OAI study protocol, OAI thigh MRI protocol components are optimized for skeletal muscle segmentation and subcutaneous and muscular fat depots assessment [19]. These MRIs were acquired using 3T MRI scanners (Trio, Siemens Healthcare, Erlangen, Germany) in 15 continuous axial T1-weighted spin-echo images, beginning 10 cm proximal to the distal femoral epiphysis. We used a publicly available validated deep learning model with a 2D U-Net structure to segment thigh muscle MRIs, with comparable results to manual segmentation on OAI thigh MRIs [20]. Details of the segmentation method, the rationale for using muscle quality biomarkers and the method for assessing CSA and adipose components of thigh muscle groups are described elsewhere [20].

In short, the axial slice corresponding to the distal 33% length of the femur bone was used for thigh muscle segmentation. The CSA of thigh muscle groups (quadriceps, flexors, adductors, and Sartorius) were directly

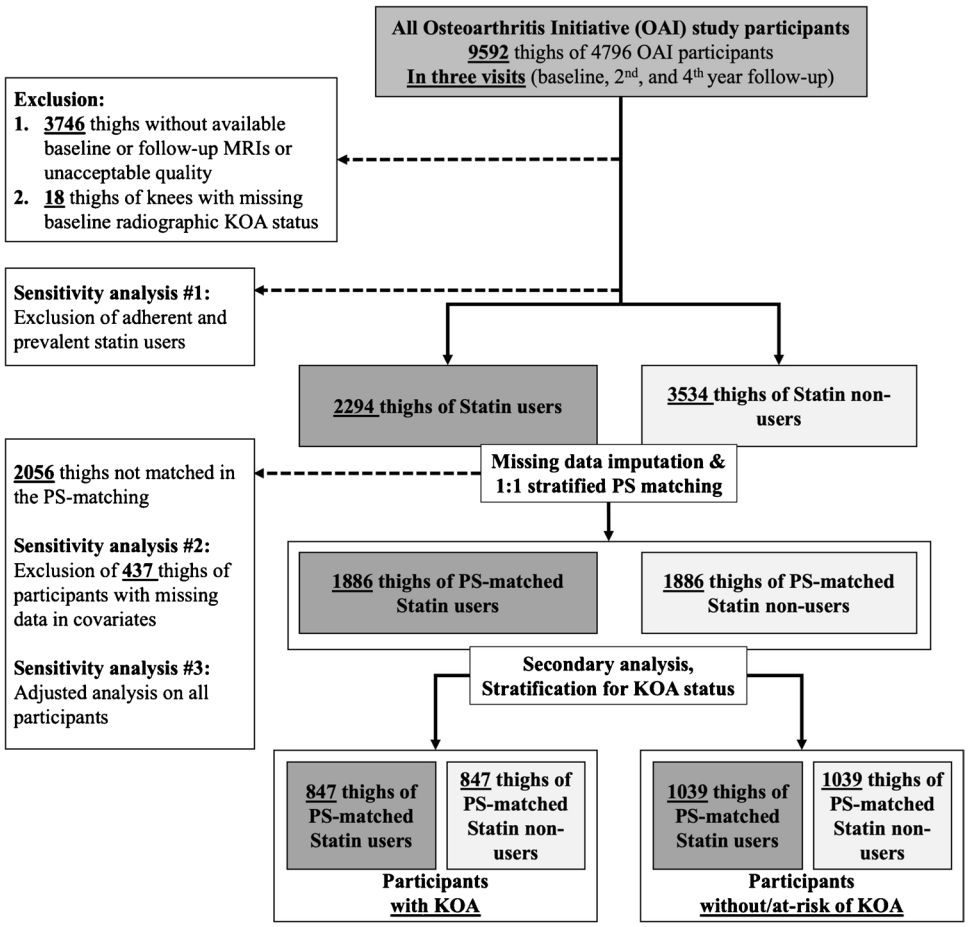

Fig. 1 Flowchart of study selection criteria and cohorts. KL, Kellgren-Lawrence; KOA, knee osteoarthritis, PS, propensity-score; OA, osteoarthritis; OAI, Osteoarthritis Initiative

calculated from segmentations and summed to calculate total thigh muscles CSA. A validated intensity thresholding method, the Otsu algorithm, was applied for estimating adipose components [21]. Intensity-based approaches on T1-weighted MRI for fat quantification, while not as accurate as water/fat-suppressed MRI protocols [22], have been extensively used in prior studies [23–25], have high inter-observer reliability, [26] strongly correlate with fat measurements by the MR spectroscopy [26], and are validated measures of muscle fat content [27]. Subsequently, we measured total thigh muscles intra-muscular adipose tissue (intra-MAT, white pixels inside muscles in T1-weighted images, by thresholding intra-muscular tissue) and total thigh muscle contractile percentage (the percentage of all thigh muscle mass, except intra-MAT) at baseline, 2nd, and 4th-year follow-up. Furthermore, we calculated specific extension and flexion contractile forces for each visit, which are the maximum muscle force per each cm^2 of quadriceps and flexor group muscles CSA, respectively [13–15].

Outcome definition

Previously validated biomarkers of muscle quality included thigh muscle CSA, intra-MAT, contractile percent, and knee flexor and extensor specific forces (force/CSA). Longitudinal 4-year changes in these measures were the study's outcomes of interest. Supplemental Fig. 1 illustrates the outcome of this study.

Data imputation and propensity score matching

We assessed the pattern of missing data (< 2.8% missing in all variables, Supplemental Table 2) and performed the multiple imputation method to estimate missing values in the confounding variables (Supplemental material). Then, using logistic regression and nearest-neighbor matching methods, we matched statin users to non-users by applying the 1:1 PS-matching for potential confounders. The matching process was stratified for the baseline KOA status (separately for patients with and without/at-risk of KOA). Potential

Table 1 Baseline characteristics of the study sample before and after propensity score matching according to statin use

	All OAI study participants' thighs[#]		*SMD*	PS-matched participants' thighs		*SMD*
	Statin (−)	Statin (+)		Statin (−)	Statin (+)	
	N: 3534	*N*: 2294		*N*: 1886	*N*: 1886	
Subject characteristics						
Age (year) (*mean* (*SD*))	59.69 (9.12)	62.75 (8.65)	**0.34**	62.15 (9.25)	62.05 (8.57)	0.01
No. of women (*N* (%))	2090 (59.2)	1168 (50.9)	**0.17**	954 (50.6)	988 (52.4)	0.04
Race, non-white (*N* (%))†	665 (18.8)	444 (19.4)	0.01	327 (17.3)	355 (18.8)	0.04
Comorbidities and risk factors						
PASE score (*mean* (*SD*))	171.94 (82.75)	154.78 (78.34)	**0.21**	157.18 (78.57)	159.9 (80.25)	0.03
BMI (kg/m^2) (*mean* (*SD*))	27.81 (4.73)	29.22 (4.42)	**0.31**	28.81 (4.88)	28.79 (4.30)	0.00
Waist circumference, (cm) (*mean* (*SD*))	100.01 (12.82)	104.06 (11.53)	**0.33**	103.03 (12.32)	102.94 (11.3)	0.01
Abdominal (central) obesity (*N* (%))*	2300 (65.1)	1696 (73.9)	**0.19**	1332 (70.6)	1349 (71.5)	0.02
Alcohol use per week (*N* (%))			0.09			0.04
None	663 (18.8)	423 (18.4)		342 (18.1)	337 (17.9)	
< 1 drink/wk	1295 (36.7)	900 (39.2)		700 (37.1)	731 (38.8)	
1–3 drinks/wk	563 (15.9)	318 (13.9)		275 (14.6)	281 (14.9)	
4–7 drinks/wk	548 (15.5)	321 (14.0)		277 (14.7)	258 (13.7)	
8–14 drinks/wk	303 (8.6)	208 (9.1)		180 (9.5)	174 (9.2)	
+ 15 drinks/wk	160 (4.5)	124 (5.4)		112 (5.9)	105 (5.6)	
Smoking (*N* (%))			**0.13**			0.04
Never smoked	2019 (57.2)	1180 (51.4)		1025 (54.3)	986 (52.3)	
Past smoker	1304 (36.9)	982 (42.8)		755 (40.0)	789 (41.8)	
Smoker < 14 cigarettes/day	139 (3.9)	80 (3.5)		66 (3.5)	67 (3.6)	
Smoker ≥ 14 cigarettes/day	70 (2.0)	52 (2.3)		40 (2.1)	44 (2.3)	
Diabetes (*N* (%))	104 (2.9)	285 (12.4)	**0.36**	100 (5.3)	128 (6.8)	0.06
Hypertension (*N* (%))	676 (19.1)	492 (21.4)	0.06	406 (21.5)	400 (21.2)	0.01
CVA (*N* (%))	65 (1.8)	89 (3.9)	**0.12**	53 (2.8)	51 (2.7)	0.01
Heart attack (*N* (%))	25 (0.7)	81 (3.5)	**0.20**	21 (1.1)	34 (1.8)	0.06
Heart failure (*N* (%))	42 (1.2)	66 (2.9)	**0.12**	31 (1.6)	24 (1.3)	0.03
Peripheral artery disease (*N* (%))	10 (0.3)	34 (1.5)	**0.13**	6 (0.3)	8 (0.4)	0.02
Malignancy (*N* (%))	118 (3.3)	98 (4.3)	0.05	69 (3.7)	75 (4.0)	0.02
Advanced liver disease (*N* (%))	10 (0.3)	2 (0.1)	0.05	4 (0.2)	0 (0.0)	0.07
Kidney dysfunction (*N* (%))	25 (0.7)	40 (1.7)	0.09	19 (1.0)	20 (1.1)	0.01
COPD (*N* (%))	67 (1.9)	63 (2.7)	0.06	47 (2.5)	40 (2.1)	0.03
Peptic ulcer (*N* (%))	84 (2.4)	67 (2.9)	0.03	37 (2.0)	38 (2.0)	0.00
Charlson Comorbidity Index (*mean* (*SD*))	0.28 (0.73)	0.50 (0.95)	**0.26**	0.32 (0.75)	0.35 (0.77)	0.05
KL grade (*N* (%))			**0.12**			0.01
Grade 0	958 (27.1)	666 (29.0)		540 (28.6)	539 (28.6)	
Grade 1	436 (12.3)	302 (13.2)		255 (13.5)	254 (13.5)	
Grade 2	98 (2.8)	64 (2.8)		52 (2.8)	54 (2.9)	
Grade 3	1414 (40.0)	792 (34.5)		650 (34.5)	658 (34.9)	
Grade 4	626 (17.7)	470 (20.5)		389 (20.6)	381 (20.2)	
OAI cohort assignment			0.05			0.09
Non-exposed control	12 (0.3)	8 (0.3)		0 (0.0)	8 (0.4)	
Incidence	2624 (74.3)	1654 (72.1)		1371 (72.7)	1376 (73.0)	
Progression	896 (25.4)	632 (27.6)		515 (27.3)	502 (26.6)	
Medications						
Diuretic (*N* (%))	524 (14.8)	594 (25.9)	**0.28**	419 (22.2)	413 (21.9)	0.01
B blocker (*N* (%))	364 (10.3)	494 (21.5)	**0.31**	302 (16.0)	326 (17.3)	0.03
Calcium channel blocker (*N* (%))	216 (6.1)	314 (13.7)	**0.26**	190 (10.1)	200 (10.6)	0.02

Table 1 (continued)

	All OAI study participants' thighs[#]		*SMD*	PS-matched participants' thighs		*SMD*
	Statin (−)	Statin (+)		Statin (−)	Statin (+)	
	N: 3534	*N*: 2294		*N*: 1886	*N*: 1886	
Non-statin lipid-lowering drug (*N* (%))	90 (2.5)	142 (6.2)	**0.18**	78 (4.1)	82 (4.3)	0.01
ACEI/ARB (*N* (%))	540 (15.3)	700 (30.5)	**0.37**	446 (23.6)	448 (23.8)	0.00
Oral hypoglycemic (*N* (%))	68 (1.9)	230 (10.0)	**0.35**	68 (3.6)	101 (5.4)	0.09
NSAIDs (*N* (%))	502 (14.2)	414 (18.0)	**0.10**	316 (16.8)	314 (16.6)	0.00
Aspirin (*N* (%))	72 (2.0)	110 (4.8)	**0.15**	62 (3.3)	64 (3.4)	0.01
SSRI (*N* (%))	230 (6.5)	236 (10.3)	**0.14**	168 (8.9)	172 (9.1)	0.01
Tricyclic antidepressant (*N* (%))	38 (1.1)	50 (2.2)	0.09	34 (1.8)	30 (1.6)	0.02
Sedative (*N* (%))	148 (4.2)	152 (6.6)	**0.11**	111 (5.9)	107 (5.7)	0.01
Systemic corticosteroid (*N* (%))	304 (8.6)	270 (11.8)	**0.11**	200 (10.6)	201 (10.7)	0.00
Thyroid hormones (*N* (%))	352 (10.0)	260 (11.3)	0.04	177 (9.4)	208 (11.0)	0.05
Antineoplastic agents (*N* (%))	72 (2.0)	68 (3.0)	0.06	51 (2.7)	51 (2.7)	0.00
Anticoagulants (*N* (%))	64 (1.8)	66 (2.9)	0.07	41 (2.2)	45 (2.4)	0.01
Muscle quality measures						
Knee extension maximum contractile force (*N*) (*mean* (*SD*))	353.32 (131.54)	352.91 (130.10)	0.00	359.34 (133.11)	355.15 (130.95)	0.03
Knee extension specific contractile force (N/cm^2) (*mean* (*SD*))	7.10 (2.01)	6.89 (1.93)	**0.10**	7.05 (2.00)	6.96 (1.91)	0.05
Knee flexion maximum contractile force (*N*) (*mean* (*SD*))	148.42 (69.24)	146.71 (69.87)	0.03	151.74 (71.32)	147.18 (70.24)	0.06
Knee flexion specific contractile force (N/cm^2) (*mean* (*SD*))	4.61 (1.79)	4.43 (1.77)	**0.11**	4.55 (1.76)	4.46 (1.75)	0.05
Total thigh muscle CSA (mm^2) (*mean* (*SD*))	9856.93 (2679.52)	10137.77 (2606.46)	**0.11**	10092.91 (2746.90)	10068.40 (2596.07)	0.01
Total thigh muscles intra-MAT CSA (mm^2) (*mean* (*SD*))	397.37 (298.47)	492.66 (330.65)	**0.30**	452.85 (330.14)	461.45 (309.51)	0.03
Total thigh muscles contractile % (*mean* (*SD*))	95.87 (2.87)	95.06 (3.16)	**0.27**	95.41 (3.03)	95.32 (3.03)	0.03

Data are presented in numbers of thighs. A significant difference for *SMD* was defined as ≥ 0.1 and is shown in bold

ACEI angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *BMI* body mass index, *CSA* cross-sectional Area, *COPD* chronic obstructive pulmonary disease, *CVA* cerebrovascular accident, *Intra-MAT* intra-muscular adipose tissue, *KL* Kellgren-Lawrence grade, *N* newton, *NSAIDs* non-steroidal anti-inflammatory drugs, *PASE* Physical Activity for Elderly Scale, *PS* propensity-score, *SMD* standardized mean difference, *SD* standard deviation, *SSRI* selective serotonin reuptake inhibitor

[#] Participants included in the sensitivity analysis #2. All OAI participants were included instead of only PS-matched participants

[†] Race of participants was categorized as white and non-white considering the small number of participants in each non-white race group

[*] Abdominal obesity was defined as a waist circumference of ≥ 94 cm in men and ≥ 80 cm in women on physical examination according to International Diabetes Foundation criteria

confounders included as covariates in the PS-matching consisted of a wide range of demographic variables, comorbid diseases, risk factors, and medications listed in Table 1 and Supplemental material. Standardized mean difference (*SMD*) was used to assess PS-matching performance between groups, where a value of ≥ 0.1 indicated an imbalance.

Sensitivity analysis

We assessed the results' sensitivity to changing statin users' selection criteria (Sensitivity analysis #1 in Fig. 1). Since SAMS are more prevalent among new and non-adherent statin users [6], to assess whether the observed changes in the muscle biomarkers are correlated with statin use itself and not the underlying conditions associated with prevalent statin use, we performed a sensitivity analysis consisting of only this group of statin-users by excluding statin users with prevalent statin use (> 30 days of statin use before baseline) and adherent statin users (continuous statin use at baseline and all annual visits). We also assessed sensitivity to data imputation (excluding 437 participants with missing data in either covariate, Sensitivity analysis #2 in Fig. 1) and PS-matching methods (by performing adjusted analysis on all included OAI participants, Sensitivity analysis #3 in Fig. 1).

Statistical analysis

We used linear mixed-effect regression models to compare the longitudinal changes in muscle biomarkers between statin users and non-users. Interaction of time and statin use was the independent variable (i.e., predictor), and total thigh muscle CSA, intra-MAT, total thigh contractile percentage, as well as maximum and specific contractile forces were the dependent variables (i.e., outcomes). Furthermore, analyses were stratified for baseline radiographic KOA (KL grade ≥ 2). We considered random intercept and slope for each cluster of matched statin user:non-user and within-subject similarities due to the inclusion of both thighs of participants. All statistical models with muscle maximum and specific contractile forces as dependent variables were adjusted for baseline knee joint pain (assessed by Western Ontario and McMaster Universities or WOMAC pain score) [28] to minimize the effect of KOA-related knee joint pain on the muscle contractile force assessments.

We assessed and addressed assumptions of linear mixed-effect regression, including linearity, homogeneity of variance, normal distribution of residuals, and normality (data were scaled and normalized in case of non-normal distribution). We further calculated the amount of minimal detectable change (MDC) for all study outcome measures. MDC is the minimal amount of change that needs to be detected in a measurement to be more than the within-subject variability and measurement error. It was calculated from fixed-effect variable (statin use in this study) β-estimate standard error of measurement (*SEM*). $MDC = SEM \times Z\,(1-\alpha) \times \sqrt{2}$, where $\alpha = 0.05$ and $Z\,(1-\alpha) = 1.96$ [29]. All statistical analyses were performed using the R software version 4.0.3 (*haven*, *MatchIt*, *mice*, *lme4*, *lmerTest*, and *tableone* packages). We used the false discovery rate (FDR) method for correcting *p*-values for multiple comparisons. A two-tailed FDR-corrected *p*-value < 0.05 was considered of statistically significant difference.

Results

Sample characteristics

A total of 9592 thighs (of 4796 participants with and without/at-risk of KOA) in the OAI were assessed for the availability of quality thigh MRI. Of 9592 thighs, 3748 thighs without quality at baseline and follow-up (2nd- or 4th-year) thigh MRIs and 18 thighs with missing KOA status at baseline (i.e., missing KL grade in the same side knee) were excluded (Exclusion #1 and #2 in Fig. 1). Based on statin use status, the remaining 5828 thigh images were classified into 2294 thighs of statin-users and 3534 thighs of non-users. After stratified PS-matching for potential confounders, 3772 pair-matched thighs of 1910 participants were included (1886 thighs of statin-users: 1886 non-users). In the PS-matched statin-users and non-users cohorts, the *mean age* $\pm$ *SD* was 62.1 ± 9.25 and 62.1 ± 8.57 years (range: 45–79), with 51% (*N*: 954) and 52% (*N*: 988) of thighs belonging to women, respectively. Among PS-matched statin users, the percentage of generic statin type was 45.2% atorvastatin, 34% simvastatin, 8.5% pravastatin, 6.5% rosuvastatin, 4.5% lovastatin, and 1.2% fluvastatin. The results also showed *SMD* < 0.1 for all variables included in the PS-matching in all participants (Table 1) or either of with and without/at-risk of KOA strata of PS-matched statin users: non-users (Supplemental Table 4). Although baseline thigh muscle measurements were not included in PS-matching, there was no statistically significant imbalance in imaging-derived muscle biomarkers between PS-matched statin-users and non-users at baseline (*SMD* < 0.1 in Table 1).

Comparison of the longitudinal changes in muscle biomarkers between statin users and non-users

Results of the mixed-effect regression models revealed no association between statin use and changes in total thigh muscle CSA (mean difference, 95% confidence interval (*CI*): 6.46 mm^2/year, -4.81–17.73). Statin use was associated with a slight decrement in maximum and specific knee extension contractile forces (-1.85 *N*/year, -3.23 to -0.47, and -0.04 *N*/cm^2/year, -0.07 to -0.01, respectively) while having no associations with knee flexion maximum (0.17 *N*/year, -0.62–0.96) and specific (-0.00 *N*/cm^2/year, -0.02–0.02) contractile forces (Table 2). In addition, results showed a slight increment in intra-MAT (3.06 mm^2/year, 0.53–5.59) and a decrease in total thigh muscles contractile percentage (-0.03%, -0.06 to -0.01) associated with statin use (Table 2). All significant results were greater than their respective MDC levels. To better demonstrate the effect size, we divided each muscle biomarker's mean difference value by its average baseline value (the "% of baseline" column in Table 2). We further assessed annual changes in muscle biomarkers in the entire OAI sample and compared the values with changes associated with statin use (Table 2). In summary, the mean difference/year between statin users and non-users was less than 1% of baseline values for all muscle biomarkers, indicating a slight association. Figure 2 illustrates changes in intra-MAT in a statin user OAI participant between baseline and 4th-year visits.

Stratification for baseline KOA status

In participants with KOA, there was no association between statin use and changes in either muscle biomarker. However, we observed a slight association between statin use and longitudinal change in all muscle

Table 2 Comparison of longitudinal changes in the muscle quality biomarkers between PS-matched statin users and non-users

	A: mean difference/year (95% *CI*), *P*	B: MCD	C: % of the baseline value	D: annual change in the muscle biomarkers in the entire OAI sample, mean difference (*SD*)	E: average changes associated with statin use over annual changes in muscle biomarkers of the entire OAI sample
Muscle contractile force					
Knee extension maximum contractile force (N)	**− 1.85 (− 3.23 to − 0.47), *P* 0.009***	1.38	− 0.52%	− 7.27 (24.45)	25.4%
Knee extension specific contractile force (N/cm^2)	**− 0.04 (− 0.07 to − 0.01), *P* 0.006***	0.03	− 0.57%	− 0.09 (0.49)	44.4%
Knee flexion maximum contractile force (N)	0.17 (− 0.62–0.96), *P* 0.677	0.79	0.11%	− 5.72 (14.37)	− 3.0%
Knee flexion specific contractile force (N/cm^2)	− 0.00 (− 0.02–0.02), *P* 0.984	0.02	0.00%	− 0.16 (0.43)	0.0%
Muscle size and composition					
Total thigh muscle CSA (mm^2)	6.46 (− 4.81–17.73), *P* 0.262	11.24	0.06%	− 54.21 (182.79)	− 11.9%
Total thigh muscle Intra-MAT CSA (mm^2)	**3.06 (0.53–5.59), *P* 0.018***	2.53	0.67%	16.16 (46.74)	18.9%
Total thigh muscles contractile %	**− 0.03 (− 0.06 to − 0.01), *P* 0.016***	0.03	− 0.03%	− 0.19 (0.47)	15.8%

Longitudinal mixed-effect regressions were used to assess the difference in muscle biomarkers between PS-matched statin users vs. non-users (column A). Minimum detectible changes were calculated as $MDC = Z(1-\alpha) \times \sqrt{2} \times$ standard error of measurements (column B). The percentages of mean difference to baseline values of each biomarker were calculated (column C). The longitudinal change in each marker during the follow-up was calculated in the entire OAI sample (column D) to estimate the percentage of changes in muscle quality markers attributable to statin use (column E). Random intercept and slope were considered for clusters of matched participants and clusters of thighs for each participant. Statistical models with muscle forces as dependent variables were adjusted for baseline knee joint pain

CSA cross-sectional area, *Intra-MAT* intra-muscular adipose tissue, *MCD* minimum detectible changes, *N* newton

* and bold values are indicative of significant *P*-values after FDR correction

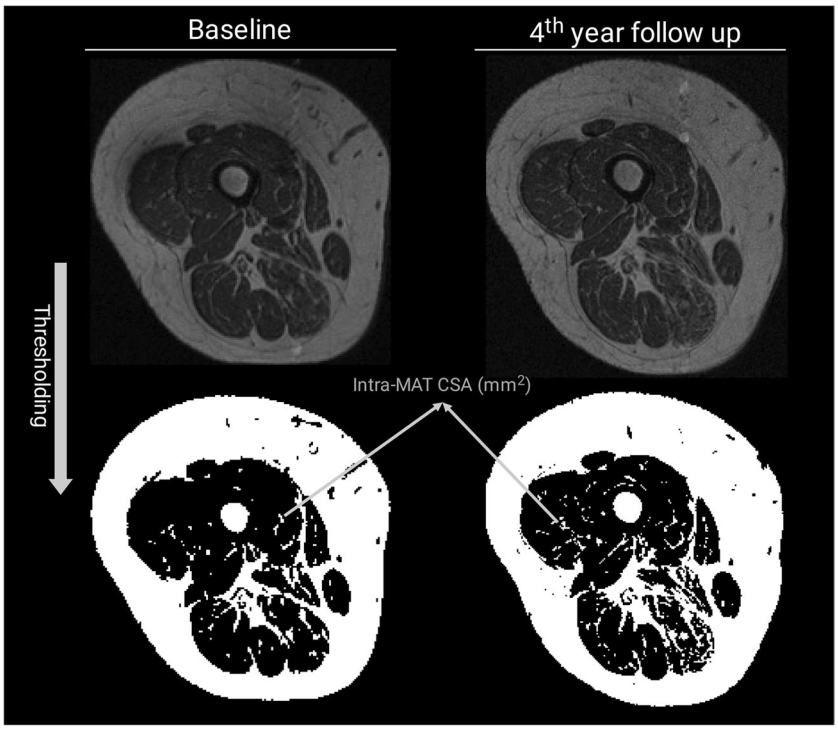

Fig. 2 Muscle quality biomarkers at baseline and 4th-year in a statin-user. Baseline and 4th-year follow-up axial MRIs of the left thigh of a 66-year-old woman with 3 years of statin use during follow-up and no baseline knee osteoarthritis (Kellgren-Lawrence grade of 0). Images show an increase in the intramuscular adipose tissue (intra-MAT) with no visible change in the cross-sectional muscle area. A decrease in muscle contractile percent can be seen. Maximum and specific knee extensor contractile forces of this participant's left knee slightly decreased during the 4-year follow-up (− 6.3 N and − 0.2 N/cm^2)

Table 3 Stratified comparison of longitudinal changes in the muscle quality biomarkers between PS-matched statin users and non-users, according to the presence of knee osteoarthritis

	With KOA PS-matched participants Average difference/year (95% *CI*), *P*	% of baseline	Without/at-risk of KOA PS-matched participants Average difference/year (95% *CI*), *P*	% of baseline	Ph
Muscle contractile force					
Knee extension maximum contractile force (*N*)	−1.54 (−3.66 to 0.57), *P*: 0.153	−0.44%	**−2.04 (−3.87 to −0.22), *P*: 0.028***	−0.56%	*Ph*: 0.745
Knee extension specific contractile force (*N*/cm^2)	−0.02 (−0.07 to 0.02), *P*: 0.235	−0.29%	**−0.05 (−0.09 to −0.01), *P*: 0.009***	**−0.7%**	*Ph*: 0.403
Knee flexion maximum contractile force (*N*)	1.12 (−0.05 to 2.29), *P*: 0.061	0.77%	−0.54 (−1.61to 0.54), *P*: 0.327	−0.35%	***Ph*: 0.042**
Knee flexion specific contractile force (*N*/cm^2)	0.03 (0.00 to 0.07), *P*: 0.043	0.70%	−0.03 (−0.06 to 0.01), *P*: 0.105	−0.64%	***Ph*: 0.010**
Muscle size and composition					
Total thigh muscle CSA (mm^2)	−9.64 (−28.14 to 8.86), *P*: 0.307	−0.09%	**19.23 (5.33 to 33.13), *P*: 0.007***	0.19%	***Ph*: 0.015**
Total thigh muscle Intra-MAT CSA (mm^2)	1.07 (−3.07 to 5.21), *P*: 0.614	0.21%	**4.52 (1.39 to 7.65), *P*: 0.005***	1.11%	*Ph*: 0.192
Total thigh muscles contractile %	−0.02 (−0.07 to 0.02), *P*: 0.265	−0.02%	**−0.04 (−0.08 to −0.00), *P*: 0.027***	−0.04%	*Ph*: 0.592

Longitudinal mixed-effect regressions were used to assess the difference in muscle biomarkers between PS-matched statin users vs. non-users. Random intercept and slope were considered for clusters of matched participants and clusters of thighs for each participant to address between-sample similarities. The percentages of mean difference to baseline values of muscle quality biomarkers are shown in the "% of baseline" column. The results of the two strata were compared using a homogeneity test. All statistical models with muscle maximum and specific contractile forces as dependent variables were adjusted for baseline knee joint pain (assessed by the Western Ontario and McMaster Universities pain score)

CSA cross-sectional area, *Intra-MAT* intra-muscular adipose tissue, *N* newton, *Ph* heterogeneity test *p* value

* Significant *P*-values after FDR correction, Bold: Significant *p*-values

biomarkers in participants without/at-risk KOA, except for knee flexion maximum and specific contractile force (Table 3). In participants without baseline KOA, statin use was associated with a slight decrement in knee extension maximum (− 2.04 N/year, − 3.87 to − 0.22) and specific (− 0.05 *N*/cm^2/year, − 0.09 to − 0.01) contractile forces. Moreover, a slight increment in total thigh muscle CSA (19.23 mm^2/year, 5.33–33.13), intra-MAT (4.52 mm^2/year, 1.39–7.65), as well as a decline in thigh muscle contractile percentage (− 0.04%/year, − 0.08 to − 0.00) were noted in association with statin use in participants without KOA at baseline (Table 3).

Sensitivity analysis

Our sensitivity analysis showed that our results were not sensitive to excluding prevalent and adherent statin users. Moreover, effect sizes for muscle quality decline were larger in the incident and non-adherent statin users (Supplemental Tables 5 and 6). The results were neither sensitive to the data imputation method nor PS-matching.

Discussion

This is the first observational longitudinal study investigating the long-term objective changes in muscle quality measures associated with statin use. We demonstrated that during a 4-year follow-up period, statin use is associated with a slight deterioration (less than 1% of baseline values for all measured muscle biomarkers) in quantitative biomarkers of muscle quality in thigh MRI. Our novel MRI-based analysis is compatible with previous studies on serum biomarkers, which suggested that statins can commonly cause mild muscle injury and slight CK elevation in the majority of statin users [9]. These results have significant importance in the population at-risk of KOA *as* KOA-related clinical outcomes may be directly affected by possible deterioration in muscle quality attributed to statin use [11, 12].

Different mechanisms have been suggested for SAMS and muscle injury. Statins are HMG-CoA reductase inhibitors, reducing cholesterol levels by suppressing the synthesis of mediators in the cascade of cholesterol synthesis

[2]. It has been suggested that lower levels of mediators in the cholesterol synthesis cascade can reduce the production of molecules involved in mitochondrial function and protein synthesis [6, 30]. As a result of statin-associated mitochondrial dysfunction, myocellular fat deposition, and muscle protein degradation can occur, even without a significant rise in CK serum levels [30]. The statin-associated fat accumulation within the muscles potentially induces metabolic changes such as insulin resistance and aggravates oxidative stress in the skeletal muscle [31]. Furthermore, mitochondrial dysfunction and protein degradation can reduce muscle contractile strength even in the absence of myositis or rhabdomyolysis [31].

In this study, we observed a slight decrease in maximum knee extension force in statin users (0.5% of baseline per year). Previous studies have reported both decreased [6, 32, 33] and similar [16] contractile strength when comparing statin users (with or without SAMS) versus non-users. Some studies attributed the decreased contractile force to lower engagement in muscle-strengthening activities [32] or reduced thigh muscle strength [33] due to SAMS [6]. Therefore, in this study, we measured specific muscle contractile force, the contractile force per each unit of muscle CSA [13–15]. We observed reduced specific contractility concurrent with unchanged muscle CSA. It is probable that intra-MAT deposition and consequent reduced contractile percent, rather than muscle atrophy, are associated with statin-associated muscle weakness. However, it is noteworthy that the changes in contractile percentage and specific contractile forces detected in our study are minimal (0.3 and 7% of 10-year changes, respectively). Considering the prominent beneficial effects of statins on reducing 50% of 10-year cardiovascular events risk and 20% of 10-year all-cause mortality risk [2], these potential slight adverse effects on muscle quality on a large scale probably have minimal clinical significance.

MRI-based quantitative biomarkers have been implemented as sensitive and reliable indicators of muscle quality and function in many other chronic conditions, such as neuromuscular disorders [25] and chronic obstructive pulmonary disease [34]. However, only a few prior case-report studies have reported muscle edema and muscle fatty infiltrations associated with statin-induced myositis and rhabdomyolysis [35, 36]. These studies have used qualitative changes and focused on cases of symptomatic statin users with clinically overt myopathies (sample sizes < 10). In a recent effort to test whether statin use is associated with beneficial effects after rotator cuff injury repair, Amit et al. observed that Goutallier fatty infiltration grades and patient-reported functional outcomes had no difference between statin users and non-users [37]. Goutallier classification is a semi-quantitative fatty infiltration grading system to determine the amount of fatty degeneration in rotator cuff muscles (grade 0: normal muscle, grade 1: some fatty streaks, grade 2: < 50% fatty muscle atrophy, grade 3: 50% fatty muscle atrophy, and grade 4: > 50% fatty muscle atrophy) [38]. Therefore, compared to our study's quantitative measurements on muscle composition in a large cohort, the Goutallier classification is probably not sensitive enough to capture the slight statin-associated muscle changes we observed in our results. Moreover, rotator cuff muscles are considerably smaller than the thigh musculature, making it difficult to detect slight changes in them. Previous studies have shown that statin use can induce both subjective muscle symptoms and serum CK rise in the absence of each other [9]. In these cases, using sensitive biomarkers of muscle MRI can more accurately quantify the changes in muscle quality, which may be used in patient consultation and to improve adherence to statin therapy.

As a large portion of elderly patients with indications for statin use are either afflicted with KOA or are at risk of developing KOA [39], in the present study, we specifically aimed to assess the association of statin use with longitudinal changes in MRI-based muscle quality measures among OAI participants. In contrast to the participants without/at-risk of KOA, we observed no statistical association between statin use and change in muscle quality biomarkers in patients with KOA. However, a similar but statistically non-significant trend in muscle quality decline was seen in patients with KOA. Prior MRI studies in KOA patients have assessed muscle composition and quality changes, suggesting atrophy and increased intra-MAT in thigh muscles, compared to participants without baseline KOA [11, 12]. As we assessed OAI data, 4-year changes attributable to statins use are slight and probably clinically unimportant compared to the overall annual changes in the muscle quality markers among the entire OAI cohort (44.4% of the changes in specific extensor contractile force and 15.3% of the changes in contractile percentage). Therefore, it is plausible that statin-associated changes in muscle biomarkers in patients with KOA were masked by muscle changes attributed to KOA regardless of the statin use status.

Although it is presumptuous that the statins have a symmetric effect on thighs, and therefore patients rather than the thighs/knees should have been used as the unit for our analyses, KOA status is commonly asymmetric among OAI participants, and given the fact that statin effect on muscle according to OA status was the main question of this study, we pursued the "thigh-based" analysis.

This study has some important limitations. First, data on the incidence of statin-associated frank rhabdomyolysis and serum CK are not available in OAI. Considering the rare incidence of statin-induced rhabdomyolysis (1 per 10,000 person-year incidence [8], i.e., less than one case in our sample size), it is unlikely that its incidence has affected our results. On the other hand, future studies are

needed to assess the correlation between serum CK levels and MRI biomarkers of muscle quality. Second, the use of OAI participants limits the generalizability of our results, and future investigations on population-based studies like the Framingham study or clinical trials may address this limitation. Third, data on statin use in the OAI database was gathered by asking participants to bring their medication bottles each visit. This approach may not provide as precise data on the duration, dosage, and persistency of statin use as the exact pill count. However, this method, which has been implemented in previous OAI studies [40], is more reliable than a self-report and is shown to result in relatively accurate measures of statin use [41], even comparable to prescription data [42]. Fourth, it is observed that different generic types of statins may have variable effects on muscle-associated side effects [43]. Most (80%) of the statin users in this study used atorvastatin and simvastatin, which are lipophilic statins perceived to be associated with higher rates of muscle-related adverse compared to hydrophilic statins such as rosuvastatin [43]. Future studies should address the differential effects of statin type on muscle quality measures to overcome this potential bias. Fifth, although we matched statin users and non-users for confounding variables, the serum lipid profile is not available in the OAI dataset, and dyslipidemia, as the main indication for statin, was not matched between statin users and non-users of this study. Several studies have shown that dyslipidemia may be associated with muscle fat deposition [44]. However, dyslipidemia in such studies was concomitant with central obesity and higher BMI, which were matched between statin users and non-users in this study. To further address this limitation, we matched statin users and non-users for other indications of statin use, including a history of cardiovascular disease, cerebrovascular accident, peripheral artery disease, and diabetes, as well as use of non-statin lipid-lowering medications. Sixth, for quantitative muscle adipose tissue segmentation and analysis, chemical shift-based water/fat MRI sequences are superior to traditional T1 MRI sequences and histogram-based thresholding methods [45]. This is due to the fact that T1 signal intensity needs to be calibrated and may not directly quantify changes in muscular adipose tissue. OAI thigh muscle imaging protocol is limited to T1 images; therefore, this study has the same limitation. To address this limitation and reduce the effect of MRI field inhomogeneity on thresholding, we used the N4ITK method for field inhomogeneity correction [46]. Finally, the interaction of statin use with many factors can probably influence the association between statin use and changes in muscle quality. While KOA status was assessed in this study, the interaction of other factors like age, sedentary lifestyle, gender, and comorbid conditions may have similar influential effects on this association [47, 48] and should be explored in future studies.

In conclusion, our results indicate statin use might be associated with slightly decreased MRI-based measures of muscle quality, indicated by reduced contractility of the extensor (quadriceps) muscle and increased intra-muscular fat deposition. Thus, based on our observations, statin use may be associated with a slight alteration in muscle quality, especially in participants at-risk of KOA. However, considering the small effect size of changes in muscle quality compared to the substantial favorable cardiovascular effects of statins in clinical practice, these muscle changes are relatively less important in overall patient care.

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Data availability The de-identified clinical and demographic information of subjects is publicly available at the osteoarthritis initiative project data repository at https://oai.nih.gov.

Declarations

Ethics approval The medical ethics review boards of the University of California, San Francisco (Approval Number: 10–00532) and the four clinical centers of Osteoarthritis Initiative project recognized the project as Health Insurance Portability and Accountability Act (HIPAA)-compliant. This project was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and all individuals gave their informed consent prior to their inclusion in the study. The authors of this manuscript certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia, and Muscle.

Patient consent Subjects have given informed consent before participating in the Osteoarthritis Initiative (OAI) project.

Conflict of interest None of the authors has any conflicting personal or financial relationships with the organization that sponsored the research (NIH) that could have influenced the results of this study. FWR is chief marketing officer and shareholder of Boston Imaging Core Lab (BICL), LLC, and consultant to Calibr — California Institute of Biomedical Research and Grünenthal GmbH. AG is a shareholder of BICL and consultant to Pfizer, TissueGene, MerckSerono, Novartis, Regeneron, and AstraZeneca. SD reported that he received funding from Toshiba Medical Systems (for consultation) and grants from GERRAF

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