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SCIENTIFIC ARTICLE

Statin use and longitudinal bone marrow lesion burden: analysis of knees without osteoarthritis from the Osteoarthritis Initiative study

Kamyar Moradi[1] · Bahram Mohajer[1] · Ali Guermazi[2] · Roham Hadidchi[1] · Soheil Mohammadi[3] · Xu Cao[4] · Mei Wan[4] · Frank W. Roemer[2,5] · Shadpour Demehri[1]

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Abstract

Objectives Knee subchondral bone marrow lesions (BMLs) are one of the hallmark features of structural osteoarthritis (OA) and are potential targets for statins' disease-modifying effect. We aimed to determine the association between statin use and longitudinal changes in magnetic resonance imaging (MRI)-based BML volume in participants without radiographic knee OA at baseline.

Methods Using the Osteoarthritis Initiative (OAI) cohort, we classified participants' knees into two categories: statin users (those who consistently used statins from baseline to the fourth year of the cohort) and non-users. We employed a 1:1 ratio propensity score (PS) matching method, adjusting for factors including age, sex, race, BMI, smoking, alcohol use, physical activity, abdominal obesity, and diabetes mellitus. We measured quantitative BML volume using a validated deep learning (DL) algorithm, applied to baseline, year-2, and year-4 intermediate-weighted fat-saturated knee MRIs. The outcome was determined by the differences in the BML volume change between statin users and non-users over the 4-year period.

Results After adjusting for potential confounders, 1502 knees were included (751 statin users and 751 non-users; mean age 63.5 ± 8.7 years, 44.5% female). A Multilevel linear mixed-effects regression model showed that statin use is associated with a smaller increase in BML volume over 4 years (time–treatment interaction effect estimates, 95% confidence interval (CI) -14.88 mm^3/year, -23.04 to -6.72, $P < 0.001$).

Conclusion In participants without baseline knee OA, continuous statin use is associated with a reduced longitudinal worsening of BML volume in the tibiofemoral joint, a known structural damage marker linked to downstream OA incidence.

Keywords Bone marrow lesion · Knee osteoarthritis · Statin

✉ Kamyar Moradi
kamyarmoradi74@gmail.com

Bahram Mohajer
mohajer.bahram@gmail.com

Ali Guermazi
guermazi@bu.edu

Roham Hadidchi
roham.rmd@gmail.com

Soheil Mohammadi
soheil.mhm@gmail.com

Xu Cao
xcao11@jhmi.edu

Mei Wan
mwan4@jhmi.edu

Frank W. Roemer
froemer@bu.edu; Frank.Roemer@uk-erlangen.de

Shadpour Demehri
sdemehr1@jhmi.edu

[1] The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, 601 N Caroline St, JHOC 3142, Baltimore, MD 21287, USA

[2] Department of Radiology, Boston University Chobanian & Avedisian School of Medicine, Boston, MA, USA

[3] School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[4] Department of Orthopedic Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[5] Department of Radiology, Universitätsklinikum Erlangen & Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany

Introduction

Subchondral bone marrow lesions (BMLs) have been linked to the onset and early progression of knee osteoarthritis (OA) [1–5]. Given that articular cartilage lacks blood vessels, it relies on synovial fluid and subchondral bone vessels for nutrient uptake and gas exchange [6]. Oxidative damage in the capillary endothelium, induced by hyperlipidemia, could potentially lead to atherosclerotic vasculopathy in the subchondral bone [7]. This could result in reduced capillary blood flow, triggering osteoclastic resorption of the subchondral bone [8], thereby contributing to the development and exacerbation of subchondral BMLs [9].

Statins, commonly prescribed lipid-lowering agents [10], are used to mitigate the risk of atherosclerosis and its associated cardiovascular events [11, 12]. While their main protective effect is against the progression of atherosclerosis in coronary and carotid arteries, statins also have "pleiotropic effects" via counteracting the damage to small capillaries supplying peripheral tissues caused by hyperlipidemia [13]. Such pleiotropic effects of statins against the progression of established radiographic knee OA have been demonstrated in some previous studies [14, 15]. Specifically, a protective effect of statins against distinct knee OA-related damage, such as BMLs, in individuals with established knee OA has been shown [16–18]. To date, no prior work has investigated the effect of statins on subchondral BMLs and their longitudinal changes in the absence of radiographic OA. If shown, it might suggest that statins possess potential in protecting knees against early pre-OA subchondral damage.

In previous research, we demonstrated that among participants with generalized OA, the use of statins was associated with a decrease in the worsening of subchondral BMLs, as measured by the manual semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) on knee magnetic resonance imaging (MRI) [16]. In the current study, we employed our recently developed and validated deep learning (DL) model to quantify subchondral BML volume and track their changes over a 4-year period [19]. Our aim is to investigate the impact of statin use on changes in BML volume in knees without radiographic knee OA.

Methods

Data source

We utilized data from the longitudinal, multicenter Osteoarthritis Initiative (OAI) cohort study, which includes 4796 participants. The study received approval from the ethics committee of OAI collaborating centers (approval code: 10–00532), and all participants provided written informed consent. The naming and version of OAI dataset files used are detailed in Supplementary Appendix 1.

Population

In accordance with OAI protocols, individuals with bilateral knee replacement surgery, inflammatory arthropathies, positive pregnancy tests, MRI contraindications, and comorbid conditions were excluded from the study. To form the study sample, knee radiographs were evaluated at baseline using the Kellgren and Lawrence (KL) grading system. Knees with a KL grade of 2 or higher were classified as having radiographic OA and were excluded (Exclusion 1 in Fig. 1). Knees without OA at baseline and without available MRI at baseline or follow-up time points (year 2 and year 4) were also excluded (Exclusion 2 in Fig. 1). Participants with intermittent statin use during the 4-year period were further excluded (Exclusion 3 in Fig. 1).

Propensity score matching

We matched the knees of participants who continuously used statins throughout the 4-year period to those who never used statins using a 1:1 propensity score (PS) matching method on the imputed dataset. The PS matching was adjusted for age, sex, race, body mass index (BMI), smoking, alcohol use, physical activity, abdominal obesity, and diabetes mellitus (Supplementary Appendix 2). The standardized mean difference (SMD) was used to evaluate matching precision between the groups, with a value of ≥ 0.1 indicating an imbalance.

Statin use status

As per the OAI protocol, participants brought their medications to baseline and annual visits. The study staff recorded all information on statin type, frequency, and duration of use at each visit, and data were documented in the OAI Medication Inventory Forms (MIFs). Participants who reported statin use consistently throughout the entire 4-year period in OAI MIFs were classified as statin users. Those who reported no statin use over the 4 years were considered as statin non-users.

Measurement of bone marrow lesion volume

MRI acquisition was performed using 3-T MRI scanners (Trio, Siemens Healthcare) as per OAI protocols [16]. We quantified BML volume in both statin users and non-users (Fig. 2), using a previously validated automated DL

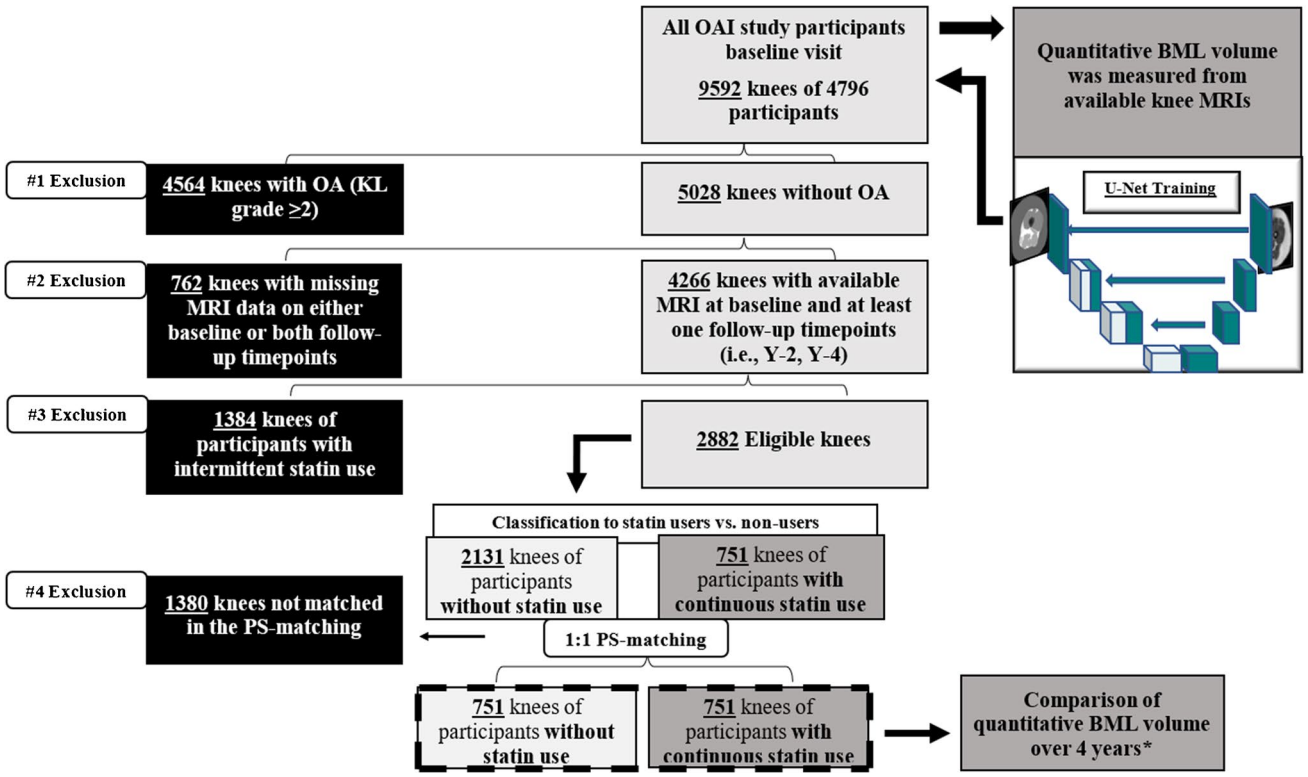

Fig. 1 Flowchart outlining the stepwise selection process. BML, bone marrow lesion; KL, Kellgren and Lawrence; OA, osteoarthritis; PS, propensity-score; Y-2, year 2; Y-4: year 4. Asterisk indicates a study outcome

model, applied to baseline, year-2, and year-4 sagittal fat-suppressed intermediate-weighted knee MRIs [19]. The outcome was defined as the total BML volume over the 4-year period across the tibiofemoral joint of the knee.

Segmentation of knee bones into subchondral plates

We used a subregion DL model to segment the bones into ten tibiofemoral subregions, similar to the MOAKS system [19]. We then defined four subchondral bone plates for the tibiofemoral joint based on a combination of the following MOAKS subregions:

- Medial femur = medial central femur + medial posterior femur
- Lateral femur = lateral central femur + lateral posterior femur
- Medial tibia = medial anterior tibia + medial central tibia + medial posterior tibia
- Lateral tibia = lateral anterior tibia + lateral central tibia + lateral posterior tibia

Statistical analysis

To minimize the biased estimates caused by excluding the missing data [20], we evaluated the missing data pattern using Little's test (< 2.1% of data; Supplementary Appendix 3) and multiple imputation method to estimate missing values in the confounding variables.

A multilevel linear mixed-effects regression model was used to compare the quantitative BML volume between PS-matched participants with and without statin use over 4 years. We considered a random intercept and slope for each cluster of PS-matched knees with and without statin use, and a random intercept for within-subjects similarities (due to the inclusion of knees from both sides in a subset of participants). The interaction between time and statin use status served as the independent predictor, while the BML volume over 4 years was the dependent outcome. As an additional analysis, we also measured the association of statin use with longitudinal BML volume changes across the four subchondral plates. All statistical analyses were performed using R software version 4.0.3 (haven, MatchIt, mice, lme4, lmerTest, and tableone packages). A two-tailed P value < 0.05 was considered statistically significant.

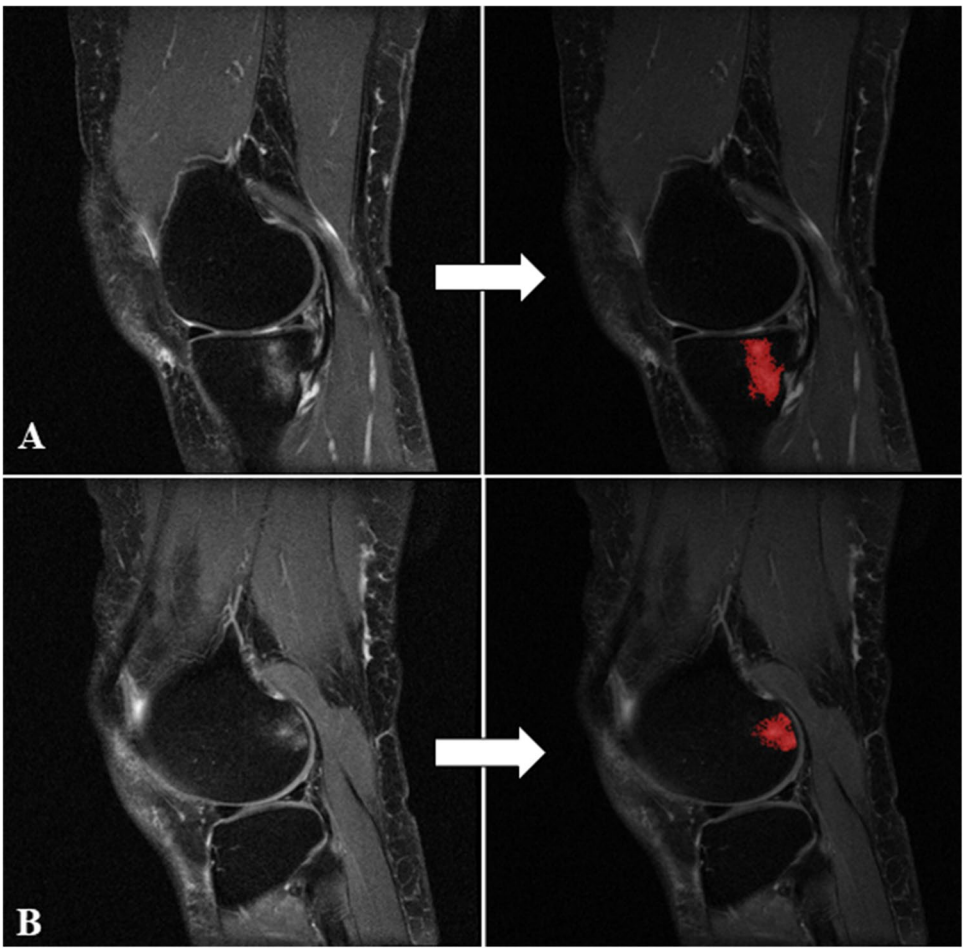

Fig. 2 Performance of the deep learning algorithm in segmenting BMLs in knees of statin users and non-users. Two examples of the model's performance in detecting BMLs: **A** BML in the medial tibia plate of the right knee of a participant with continuous statin use and **B** BML in the lateral femur plate of the right knee of a participant with no statin use

Results

Sample characteristics

Out of 9592 knees of 4796 OAI participants, 5028 knees were OA-free (KL grade < 2) at baseline and, therefore, were included (Exclusion 1 in Fig. 1). Of these, 762 knees without available MRI at either baseline or both follow-ups (second and fourth years) were excluded (Exclusion 2 in Fig. 1). One thousand three hundred eighty-four of remaining knees were excluded due to intermittent statin use of their corresponding participants during the 4 years of follow-up (Exclusion 3 in Fig. 1).

Based on statin use status, the remaining 2882 MRIs were classified into 751 knees of continuous statin users and 2131 knees of non-users. After stratified PS matching for potential confounders, 1502 pair-matched knees were included (751 knees of statin-users:751 non-users). In the PS-matched knees, the mean age ± standard deviation (SD) was 63.5 ± 8.7, with 44.5% of knees ($N = 668$) belonging to females. The results also showed SMD < 0.1 for all variables included in the PS matching in all participants (Table 1).

Although baseline BML volume measurements were not included in PS matching, there was no statistically significant imbalance in this biomarker between PS-matched statin users and non-users at baseline (SMD < 0.1 in Table 1).

Association between statin use and overall BML volume changes over 4 years

Results of the mixed-effects regression models showed that overall mean BML volume increases over 4 years (time effect estimate, 95% confidence interval (CI) 28.98 mm^3/year, 20.40 to 37.59, $P < 0.001$). Meanwhile, statin use was associated with a lesser degree of BML volume increase over this time period (time–treatment interaction effect estimate, 95% CI − 14.88 mm^3/year, − 23.04 to − 6.72, $P < 0.001$) (Fig. 3). In a supplementary analysis, we demonstrated that a 1 SD increase in BML volume was associated with a significant rise in the WOMAC pain score, with a time–treatment interaction effect estimate of 0.42/year (95% CI 0.25 to 0.59, $P < 0.001$).

Table 1 Baseline characteristics of the study sample before and after propensity score matching according to statin use over 4 years

Variables	All OAI study participants' knees			PS-matched participants' knees (1:1 ratio)		
	Statin non-users (*N* = 2131)	Statin users (*N* = 751)	SMD	Statin non-users (*N* = 751)	Statin users (*N* = 751)	SMD
Subject characteristics						
Age (years) (mean (SD))	60.34 (8.97)	63.54 (8.52)	*0.366*	63.61 (8.81)	63.54 (8.52)	0.008
Sex (female %)	1405 (65.9)	338 (45.0)	*0.431*	334 (44.5)	338 (45.0)	0.011
BMI (kg/m^2) (mean (SD))	27.45 (4.64)	28.38 (3.94)	*0.217*	28.61 (4.41)	28.38 (3.94)	0.056
Race (White) (*N* (%))[a]	1838 (86.3)	664 (88.4)	0.065	669 (89.1)	664 (88.4)	0.021
PASE score (mean (SD))	161.68 (81.31)	157.92 (78.32)	0.047	154.88 (78.44)	157.92 (78.32)	0.039
Smoking status (*N* (%))	389 (18.3)	214 (28.5)	*0.244*	201 (26.8)	214 (28.5)	0.039
Alcohol use (≥ 1/week) (*N* (%))	961 (45.1)	320 (42.6)	0.050	313 (41.7)	320 (42.6)	0.019
Abdominal (central) obesity (*N* (%))[b]	1843 (86.5)	665 (88.5)	0.062	658 (87.6)	665 (88.5)	0.029
Diabetes (*N* (%))	98 (4.6)	115 (15.3)	*0.364*	122 (16.3)	115 (15.3)	0.045
BML volume (mean (SD))[c]	31.89 (107.71)	37.39 (153.65)	0.041	42.18 (146.30)	37.39 (153.65)	0.032

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

BMI body mass index, *BML* bone marrow lesion, *N* number, *PASE* Physical Activity for Elderly Scale, *PS* propensity score, *SMD* standardized mean difference, *SD* standard deviation

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

[b]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

[c]Not included in the PS matching

Association between statin use and BML volume changes over 4 years according to distinct subchondral plates

We analyzed the association of continuous statin use with 4-year BML volume change in the four subchondral plates (medial femur, lateral femur, medial tibia, and lateral tibia). Knees of participants with statin use had a lesser degree of BML volume increase in lateral femur (time–treatment interaction effect estimate, 95% CI − 4.62 m^3/year, − 8.91 to − 0.30, $P = 0.035$), medial tibia (time–treatment interaction effect estimate, 95% CI − 2.37 mm^3/year, − 4.53 to − 0.24, $P = 0.029$), and lateral tibia (time–treatment interaction effect estimate, 95% CI − 4.44 mm^3/year, − 7.08 to − 1.80, $P < 0.001$) (Table 2).

Discussion

Our results show that statin use is associated with a reduced rate of increase in subchondral BML volume in knees without OA at baseline. Given the comprehensive matching for potential cofounders, it is less likely that these results are attributed to the baseline BML volume or known demographics and clinical risk factors of knee OA. Thus, our observational data suggest that continuous statin use is associated with a reduction in the rate of BML progression with possibility of decrease risk of OA.

Prior studies have predominantly concentrated on the impact of statins on the progression of pre-existing knee OA [21–29]. The influence of statins on subchondral BMLs, a risk factor for OA, has been explored in three previous studies [16–18]. Two of these studies found no effect, while one showed a protective effect of statins on BML progression, potentially due to different subject selection criteria. All three studies included participants with baseline knee OA. While these previous studies employed semi-quantitative methods to monitor BML progression, our current study utilized a fully quantitative DL model. Our developed model automatically segments and quantifies BML volumes, thereby eliminating intra- and inter-observer variability. This allows tracking of longitudinal changes of knee MRI in large sample size ($N = 1502$) and with longer follow-up periods (4 years). We propose that the use of statins primarily prescribed for cardiovascular diseases may offer the secondary advantage of reducing the progression of subchondral BMLs [30]. Although statins can negatively impact thigh muscle quality [31], which may heighten the risk of knee OA [32], our prior research has demonstrated this effect to be minimal [33]. Further clinical and experimental studies are warranted to investigate and confirm the protective role of statins against subchondral BMLs in early OA stages.

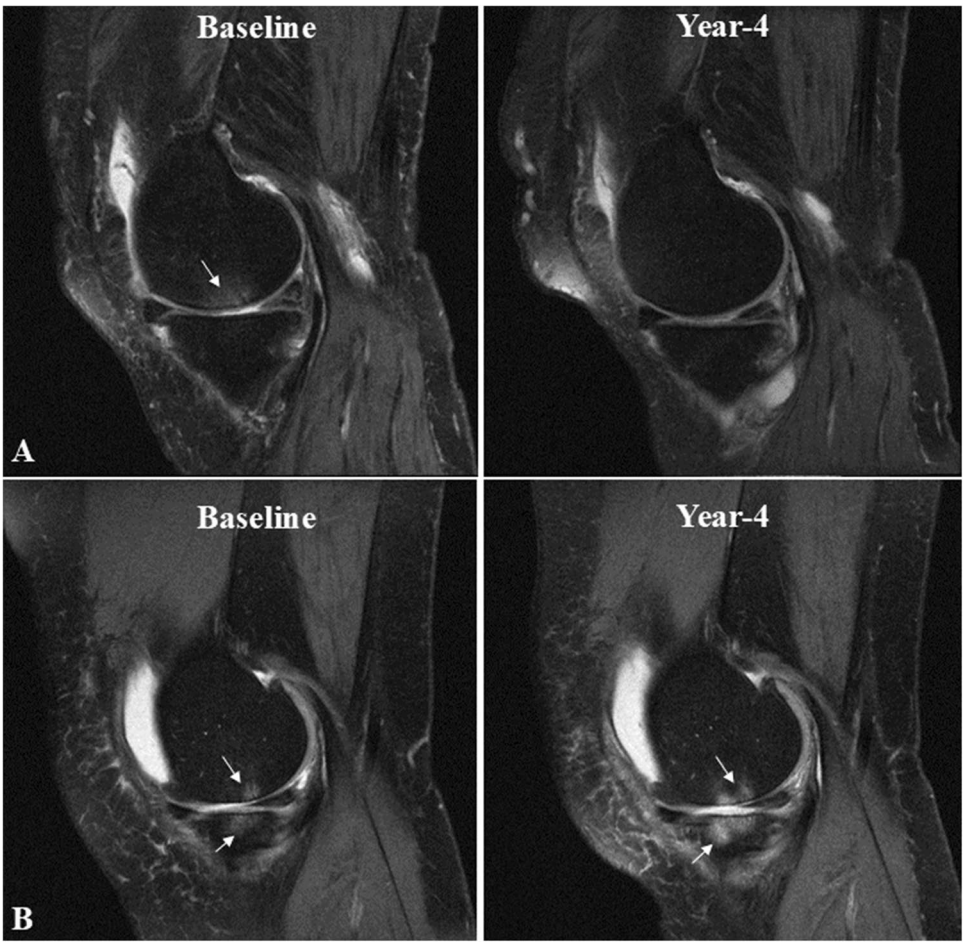

Fig. 3 Changes in BML volume over 4 years in non-OA knees of statin users compared to non-users. Two examples of BML volume change over 4 years: **A** reduction in BML volume in the right knee of a participant with continuous statin use and **B** increase in BML volume in the propensity score-matched right knee of a participant without statin use

Table 2 The association of continuous statin use with bone marrow lesion (BML) volume change over 4 years across different subchondral plates

Subchondral plate	Change rate difference (mm^3) per year (95% CI)[a]	*P* value
Medial femur	−2.52 mm^3/year (−6.42 to 1.35)	0.201
Lateral femur	−4.62 m^3/year (−8.91 to −0.30)	*0.035*
Medial tibia	−2.37 mm^3/year (−4.53 to −0.24)	*0.029*
Lateral tibia	−4.44 mm^3/year (−7.08 to −1.80)	*< 0.001*

[a]Multilevel longitudinal mixed-effects regressions were used to assess the difference in BML volume between the propensity score–matched statin users vs. non-users, and the time–treatment interaction was reported

CI confidence interval

The pleiotropic effect of statins may be explained via its serum lipid–lowering effect given the known impact of hyperlipidemia on subchondral bone. In mouse models, increased angiogenesis and blood vessel volume are critical factors driving the progression of OA [34, 35]. By managing high blood lipid concentrations, the oxidative damage to the capillaries that supply the subchondral knee bone marrow is lessened [7, 8, 13, 36]. Statins mitigate the ischemic effect on bone marrow induced by hyperlipidemia, thus decreasing osteoclastic resorption [37] and the progression of subchondral BMLs [38]. Furthermore, statins provide protection against damage to the capillary endothelium [36], osteonecrosis [38], and bone deterioration [39].

This study has several limitations. First, we did not have access to the exact duration, dose, and intensity of statin use, which may have a confounding effect on the findings. Nevertheless, OAI staff confirmed the prescription for statins according to medications participants brought with them during visits. While this data cannot be used to explore the dose-dependent effects of statins, it is more reliable than self-reported measures of medication use [40] and has been employed in previous OAI studies [15, 16, 26, 29]. Second, the statin group included statin users with variable duration of use before the baseline visit (both prevalent and incident users). This increases the risk of Neyman bias, which is a selection bias in which very sick or healthy participants are excluded due to chronic disease [41]. Third, our analysis is limited due to its retrospective nature. MRI data came from a collection of a nested case–control studies within the OAI, many of which had

their own specific inclusion and exclusion criteria. Our detailed selection criteria and PS matching addressed this limitation. However, it is important to note that lifestyle confounding factors, which were adjusted for at baseline, may change over the 4-year period, and the study does not account for these changes. Lastly, we did not have access to each participant's lipid profile, which is a common indicator of statin use [42]. However, we matched participants according to other statin indications (such as cardiovascular disease).

In conclusion, statins may protect against subchondral BML incidence and progression in those without pre-existing knee OA. While our previous works have shown statins to have this effect on knees with baseline OA [16], this study extends this finding to knees without OA, suggesting that statins possess a potential in protecting against early pre-OA subchondral damage. Future studies are warranted in investigating the mechanisms mediating the effects of statins on BML volume over time.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00256-025-04878-6.

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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. The R codes used in this work are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate 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. Subjects have given informed consent before participating in the Osteoarthritis Initiative (OAI) project. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Competing interests AG is a shareholder of BICL and consultant to Pfizer, TissueGene, Novartis, Coval, ICM, TrialSpark, and Medipost. FWR is shareholder of BICL and LLC, and consultant to Grünenthal GmbH. SD reported that he received funding from Toshiba Medical Systems (for consultation) and grants from GERRAF and Carestream Health (for a clinical trial study). The views expressed are those of the authors and not those of the National Health Service, the NIHR, or the Department of Health. None of the authors has any conflicting personal or financial relationships that could have influenced the results of this study. The other authors declare no competing interests.

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