Association of Statin Use and Development and Progression of Hip Osteoarthritis in Elderly Women

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ABSTRACT. ***Objective***. To examine the association between use of HMG CoA reductase inhibitor (statin) and development and progression of radiographic findings of hip osteoarthritis (OA) in elderly women.
Methods. Baseline and followup anteroposterior pelvic radiographs were obtained, a mean of 8 years apart, in 5674 women (69% of the total survivors) age 65 years and older from the Study of Osteoporotic Fractures. Hips were scored for individual radiographic features (IRF) and assigned a summary grade of radiographic hip osteoarthritis (RHOA) based on the number and type of IRF present. Statin use was recorded from prescription labels provided by participants at Year 6 and Year 8 of followup. We estimated odds ratios for the development of RHOA in hips without disease at baseline and for progression of RHOA in hips with baseline disease, using generalized estimating equations to account for correlations of right and left hips.
Results. RHOA was present in 936 hips of 745 women at baseline and there were 9318 hips without baseline RHOA. Overall, 7% of women in this cohort were statin users. Statin use was associated with increased odds of developing incident summary grade ≥ 3 RHOA (OR 1.92, 95% CI 1.03–4.43, p = 0.045), but was not significantly related to other measures of new RHOA. In hips with baseline RHOA there was a consistent but nonsignificant trend toward decreased progression of RHOA in statin users (all OR between 0.69 and 0.76, with 95% CI between 0.29 and 1.67).
Conclusion. Statin use may be associated with an increased risk of developing incident RHOA but does not adversely influence progression of established disease. (J Rheumatol 2005;32:106–10)

Key Indexing Terms:
STATIN HIP OSTEOARTHRITIS PROGRESSION

In addition to their cholesterol lowering effects, HMG CoA reductase inhibitors (statins) are becoming recognized for their antiinflammatory and bone metabolism effects[1-4]. Exposure to statins has been associated with decreased osteoporosis in animal models, and in clinical observations[5–8] with improvement in Alzheimer's disease[9,10], decreased sepsis[11], and plaque stabilization during acute coronary syndromes[12]. The mechanisms underlying these associations are likely multifactorial and may involve effects on cytokines and other mediators of inflammation[13-15]. It has also been shown that statin use increases the production of nitric oxide (NO)[16,17].

The effects of statins on osteoarthritis (OA) are unknown, but many patients taking statins for their cardioprotective effects have or are at for risk of developing OA. Since OA is associated in some individuals with low grade inflammation, statins could decrease OA via antiinflammatory mechanisms. Alternatively, by increasing NO, statins could have a deleterious effect on OA. Recent studies have shown that NO production may inhibit cartilage matrix synthesis, shorten chondrocyte lifespan, and increase cartilage breakdown through metalloproteinase activation[16,18,19].

Nitrate use has recently been associated with increased bone mass in elderly white women[20,21], and statin use has been associated with reduced risk of osteoporotic fractures[22]. Nitrates and statins are examples of medications designed for nonrheumatologic conditions that may have effects on the bones and joint tissue metabolism.

To investigate the effect of statins on OA, we compared the development and progression of radiographic hip OA (RHOA) in statin users and nonusers in elderly Caucasian women enrolled in the Study of Osteoporotic Fractures (SOF).

MATERIALS AND METHODS

Population. Participants were in the Study of Osteoporotic Fractures, a multicenter cohort study initiated in 1986 to determine the risk factors for osteoporotic fractures in 9704 women. Participants were all age 65 years and older at baseline and were recruited between September 1986 and October 1988 from population based listings in 4 areas of the United States: Baltimore, MD, Minneapolis, MN, Portland, OR, and the Monongahela Valley near Pittsburgh, PA[23]. Nonwhite women were excluded from the original cohort because of their low incidence of hip fracture, as were

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women who were nonambulatory or who had undergone bilateral hip replacement[23]. In addition, women were excluded if they had radiographically confirmed rheumatoid arthritis (RA), Paget's disease, hip fracture, or bilateral total hip joint replacement at baseline.

Radiography and interpretation. At the baseline and followup visits, supine anteroposterior radiographs of the pelvis were obtained using a standard protocol[22,23].

Radiographs were assessed for individual radiographic features (IRF) of hip OA using atlas photographs to improve the reliability of the readings[24-27]. Minimum joint space (MJS) was measured using published methods[28]. The methods for radiographic interpretation were as described[26-30]. Radiograph pairs were initially read and measured by one primary reader (NEL) working alongside the reader blinded to the order by masking identifying information and randomly assigning the order of radiographs. Radiograph pairs with either definite osteophytes or definite narrowing (score > 2) in any location on the initial reading were jointly evaluated by 2 readers to reach consensus scoring and consensus MJS measurement[26]. A total of 21% of the radiograph pairs underwent a consensus reading. Interrater reliability for the radiograph readings evaluated from a random sample of 178 pairs was good to excellent[26].

Definitions of radiographic hip OA and radiographic progression. A summary grade of 0–4 (modified Croft grade) was assigned to each hip based on individual radiographic features[27,29]. Grade 2 required the presence of either definite joint space narrowing or definite osteophytes plus at least one other of the 5 features. Grade 3 required the presence of either definite osteophytes or joint space narrowing plus at least 2 other features. Grade 4 hips met the criteria for grade 3 plus deformity.

Hips were considered to have baseline radiographic findings of hip OA if any of the following 5 findings were present: a summary grade $\geq$ 2; a MJS of $\leq$ 1.5 mm; joint space narrowing superolaterally grade $\geq$ 2 or superomedially $\geq$ 3; or definite osteophytes in any location[30]. For analysis, hips were divided into those with and those without baseline findings of RHOA. Those without RHOA were eligible to develop RHOA. Hips with baseline RHOA were eligible for progression. A hip was defined as having developed OA if any of the above 5 findings were present on the 8-year followup radiograph in a hip free of all of these findings at baseline. A hip was defined as having progressed radiographically if any of the following occurred between baseline and followup: a decrease in MJS of $\geq$ 0.5 mm for hips with a baseline MJS $\geq$ 0.5 mm[30]; an increase of $\geq$ 1 in the summary grade; or an increase of $\geq$ 2 in total osteophyte score. Total hip replacement for OA between baseline and the Year 8 followup was assessed by radiography and review of the medical records. Changes in MJS in hips that underwent total hip arthroplasty (THA) prior to the followup radiograph were imputed using published data[31].

Assessment of potential confounders. All participants completed self-administered questionnaires at baseline that assessed age, self-reported health status, hours sedentary each day, education levels, and current medication use. Physical activity was assessed with a modified Paffenbarger Survey[32]. Height was measured on a wall-mounted Harpenden stadiometer, and weight was measured with a balance-beam scale[23,26]. Calcaneal bone mineral density (BMD) was measured at the baseline examination using single-photon absorptiometry (OsteoAnalyzers; Siemens-Osteon, Wahiawa, HI, USA). Blood pressure was also obtained at every visit. Protocols for BMD and blood pressure measurements in the SOF were as described[20,30].

Assessment of statin use. Participants attending the Year 6 and Year 8 clinic visits were asked to bring all current prescription and nonprescription medications (any use within the past 2 weeks) with them to the clinic. Medication interviews were completed by an interviewer who obtained information for each medication, including type, dose, and pattern of use (regular or as needed). Women who completed home visits during either examination had the medication history performed by an interviewer at the participant's residence. A computerized dictionary was used to categorize type of medication from product brand and generic names obtained from containers or from participant report[33]. Statin use was defined as taking any available prescription oral statins. Women who reported any statin use at Year 6 and/or Year 8 were classified as statin users.

Statistical analysis. The distribution of demographic characteristics, body composition variables, and statin use were compared between the subjects with no hip OA at baseline and women with baseline radiographic hip OA using Student's t test and chi-squared tests.

For the analysis of statin use and the development of RHOA we focused on hips without RHOA at baseline, including unaffected hips in subjects with unilateral RHOA. For the analysis of the effect of statins on progression, we included all hips with RHOA at baseline. Logistic regression analysis was used to estimate adjusted odds ratios (OR) for the dichotomous outcomes of incident radiographic findings and radiographic progression using each of the definitions. These analyses were performed in SAS (SAS Institute, Cary, NC, USA) using the generalized estimating equation method to adjust for the correlation between a subject's right and left hips when 2 hips were analyzed in order to obtain adjusted confidence intervals (CI). The statin-use variables were entered in the model as none or any-use. All analyses were performed adjusting for age, weight, height, estrogen use, vitamin D supplement use, smoking, hypertension, health status, nitrate use, and calcaneal BMD. Statistical significance was inferred when the p value was less than 0.05.

RESULTS

A total of 5987 subjects had both baseline and followup pelvic radiographs. After excluding subjects with RA, Paget's disease, bilateral total hip replacements, previous hip fracture, incomplete statin use data, and bilateral radiographic findings of OA at baseline, a total of 5674 subjects were included in this study. Study subjects at baseline had a mean age of 70.6 years (SD 4.6), mean body mass index (BMI) of 26.6 (SD 4.5), and hip pain was present in 36%. Overall, 7% of subjects were statin users. Women with no RHOA at baseline who used statins were significantly younger and heavier than nonstatin users (data not shown). Women with RHOA at baseline were significantly older, less likely to walk for exercise, and more likely to have self-reported hip pain and poorer health status compared to women without RHOA at baseline (Table 1).

Development of RHOA. At baseline, 4933 women had no RHOA in either hip. At the fifth followup visit, 566 women had developed incident RHOA in 630 hips.

Of the 5 measures of new RHOA (Table 2), only development of severe disease (summary grade $\geq$ 3) showed a significant association with exposure to statins, with users having an almost 2-fold increase in risk compared to nonusers. The other measures of RHOA development showed small, nonsignificant increases in risk among statin users. Total hip arthroplasty for OA occurred in 27 hips during the 8 years of followup. No association was seen between statin use and a composite outcome combining all new radiographic findings of OA or THA.

Progression of RHOA. At baseline, 745 women had RHOA in 936 hips. During followup, 484 hips in 420 women worsened according to at least one definition of RHOA progression. In addition, there were 97 hips in this group that underwent THA between baseline and the Year 8 examination.

Table 1. Subject characteristics by baseline hip OA status* (mean ± SD).

	All, n = 5678	Without Radiographic Hip OA at Baseline, n = 4933	With Radiographic Hip OA at Baseline, n = 745	p†
Age, yrs	78.5 (4.7)	78.3 (4.5)	79.7 (5.2)	< 0.0001
BMI, kg/m^2	26.5 (4.7)	26.5 (4.8)	26.8 (4.7)	0.217
Multivitamin with vitamin D (yes/no)	46.4	46.4	46.3	0.977
Walking for exercise (yes/no)	41.4	42.3	35.3	0.0001
Self-reported health status, % good or excellent	81.0	81.8	75.8	< 0.0001
Calcaneal BMD	0.41 (0.09)	0.41 (0.09)	0.42 (0.09)	0.190
Hip pain**	36.0	34.4	46.7	< 0.0001
Any statin use, %	6.8	6.9	7.4	0.86
No statin use, %	93.2	93.1	93.6	

* Person-based analyses. ** Hip pain was determined by self-report or physical examination, in either right or left hip. † p value from t test (for continuous variables) and chi-square tests (for categorical variables). Tests compare the characteristics by baseline OA status.

Table 2. Relationship of statin use to measures of development of radiographic hip OA* (number of hips = 9318).

	Incident JSN, % Incident OA	Osteophytes, % Incident OA	Summary Grade ≥ 2, % Incident OA	Summary Grade ≥ 3, % Incident OA	Any OA or THA**, % Incident OA
Statin users at visit 4 or 5	3.3 (n = 21)	4.5 (n = 29)	4.2 (n = 27)	2.5 (n = 16)	7.6 (n = 49)
Nonstatin users at visit 4 or 5	3.1 (n = 268)	3.9 (n = 335)	3.3 (n = 284)	1.3 (n = 109)	7.0 (n = 608)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Risk of incident OA for any statin user	1.17 (0.89, 2.39) p = 0.134	1.28 (0.83, 2.56) p = 0.187	1.39 (0.82, 2.40) p = 0.347	1.92 (1.03, 4.43) p = 0.045	1.25 (0.90, 1.85) p = 0.264

* All analyses are adjusted for covariates: age, height, weight, vitamin D intake, baseline BMD, baseline health status, baseline smoking, hypertension, nitrate use, and estrogen use. ** 27 hips undergoing total hip arthroplasty (THA).

Women with progressive RHOA findings were less likely to be taking a multivitamin with vitamin D (42.6% vs 51.1%; p = 0.022) compared to "nonprogressors." Otherwise, there was no difference in age, BMI, walking for exercise, or other covariates between the 2 groups. Of the 4 measures of progressive RHOA (Table 3), all showed moderate but nonsignificant trends toward a decreased risk of progression in statin users. Due to the small number of statin users in the progression group (n = 26), no OR reached statistical significance.

DISCUSSION

In this study of elderly white women, statin use was associated with an increased risk for development of new relative-

Table 3. Relationship of statin use and progression of RHOA* (number of hips = 936).

	Increase in Summary Grade ≥ 1 or THA, % Progression	Decrease MJS ≥ 0.5 mm, % Progression	Increase in Osteophyte Score ≥ 2**, % Progression	Any Radiographic Progression or THA†, % Progression
Statin users at visit 4 or 5	22.4 (n = 13)	30.4 (n = 17)	15.5 (n = 9)	44.1 (n = 26)
Nonstatin users at visit 4 or 5	32.0 (n = 277)	39.5 (n = 336)	22.6 (n = 194)	52.2 (n = 458)
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Risk of OA progression for any statin user	0.76 (0.37, 1.57) p = 0.463	0.69 (0.34, 1.39) p = 0.297	0.71 (0.29, 1.67) p = 0.429	0.76 (0.41, 1.40) p = 0.384

* All analyses are adjusted for covariates: age, weight, vitamin D intake, baseline radiographic OA severity, baseline health status, baseline smoking, hypertension, nitrate use, and estrogen use. ** Excludes 97 hips undergoing total hip arthroplasty (THA). † Any radiographic progression includes increase in summary grade ≥ 1, THA, decrease MJS ≥ 0.5 mm, or increase in osteophyte score ≥ 2.

ly severe RHOA (summary grade 3 or greater), but not with other measures of new RHOA, after adjusting for potential confounding variables. Statin use was also associated with a modest but not statistically significant decrease in the structural progression of RHOA.

One hypothesis to explain the possible increase in RHOA among statin users is that statins, through stimulation of endothelial NO synthase (eNOS), increase vascular NO production that can lead to increased production of vascular endothelial growth factor (VEGF) and bone morphogenic proteins (BMP), both associated with new bone formation[34–36] and angiogenesis. If statins stimulate BMP-2 and VEGF induced bone formation in OA, the new bone may present as subchondral plate thickening or new osteophyte formation adjacent to the OA joint. The new subchondral bone around the OA joint could accelerate cartilage degeneration[6-8,37]. It is also possible that statin use in this population is associated with an unmeasured variable that causes increased RHOA. Finally, the association of statin use and incident RHOA could be from chance, but there was a consistent, though nonsignificant, trend toward increased development of RHOA observed for the other 4 measurements of new RHOA.

It is possible that the effects of statins on the progression of existing OA differ from their effect on new development of OA[38]. For example, the antiinflammatory effects of statins could slow the progression of RHOA. Of the 4 measures of RHOA progression, all had OR between 0.69 and 0.76, indicating a decreased risk of progression in statin users that could be clinically significant, but none achieved statistical significance. The small number of statin users in the group of OA progressors (n = 26) clearly limits our power in these analyses, as indicated by the relatively wide 95% confidence intervals. Statins quell inflammatory mediators[39], reducing C-reactive protein concentrations in the systemic circulation, and synovial tissues may benefit from the antiinflammatory effect in subjects with OA. In addition, statins inhibit NO produced by inducible NOS (iNOS), a key enzyme in the synovial cells and cartilage that promotes the catabolic effects of NO[40,41]. Data from animal models of OA show increased NO production by iNOS activates metalloproteinase enzymes[40,42] and treatment with anti-NO agents prevents joint destruction in OA[43]. We previously examined nitrate use in this same cohort of elderly women and found similar increases in the incidence of RHOA associated with nitrate use, possibly related to the increase in NO production associated with nitrates as well[44]. Since this may have clinical significance, it will be important to study this association in an observational study or clinical trial involving larger numbers of statin users.

This study has several important limitations. Although the SOF is an established cohort with excellent followup, it included only elderly Caucasian women, and only 7% of this population was using statins at either visit 4 or visit 5. The small number of women with both RHOA and statin use in this cohort limits the power of the study. Detailed information on statin use was only available for Years 6 and 8 (visits 4 and 5). Only half of statin users reported taking them at both visits, while the other half reported use at only one visit, too small a difference in known duration of use (one year), to evaluate the effect of the duration of use on either incidence or progression of RHOA. In addition, we did not have valid information regarding some potentially important comorbidities and confounding variables[45], including an assessment of diabetes mellitus with a fasting blood sugar and serum cholesterol levels.

Our results suggest that elderly Caucasian women using statins may have a very modest increase in the risk of developing new radiographic findings of hip OA. However, in women who already have radiographic hip OA, statins are not associated with worsening of structural disease. Our findings need confirmation in other cohort studies.

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