Association Between Cortical Bone Microstructure and Statin Use in Older Women

Berit A. M. Larsson,[1] Daniel Sundh,[1] Dan Mellström,[1,2] Kristian F. Axelsson,[1,3] Anna G. Nilsson,[1,4] and Mattias Lorentzon[1,2]

[1]Geriatric Medicine, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, University of Gothenburg, 413 45 Göteborg Gothenburg, Sweden; [2]Geriatric Medicine, Sahlgrenska University Hospital, 431 80 Mölndal Mölndal, Sweden; [3]Department of Orthopaedic Surgery, Skaraborg Hospital, 413 45 Göteborg Skövde, Sweden; and [4]Department of Endocrinology, Sahlgrenska University Hospital, 413 45 Göteborg Gothenburg, Sweden

ORCiD numbers: 0000-0003-0749-1431 (M. Lorentzon).

Context: Treatment with statins has been associated with increased bone mineral density, but whether this association depends on differences in cortical or trabecular volumetric bone microstructure is unknown.

Objective: The aim of this study was to investigate if treatment with statins is associated with bone microstructure and geometry in older women.

Design Setting and Participants: Older women were included in a population-based study of 3028 women (mean age ± SD, 77.8 ± 1.6 years) from the greater Gothenburg area in Sweden. Information regarding medical history, medication, and lifestyle factors was obtained from validated questionnaires.

Main Outcome: Bone geometry and microstructure were measured at the ultradistal and distal (14%) site of radius and tibia using high-resolution peripheral quantitative computed tomography.

Results: The 803 women in the cohort who used statins had higher body weight, worse physical function, and more frequent cardiovascular disease and diabetes than nonusers ($P < 0.05$). Statin users had lower cortical porosity (radius, 2.2 ± 1.9 vs 2.5 ± 2.0%; tibia, 5.2 ± 2.4 vs 5.4 ± 2.5; $P = 0.01$), higher cortical bone density (radius, 1008 ± 39.1 vs 1001 ± 38.4 mg/cm^3; tibia, 919 ± 42.6 vs 914 ± 41.5; $P < 0.01$), and greater cortical area (radius, 60.5 ± 9.6 vs 58.6 ± 9.7 mm^2; tibia, 150.0 ± 23.6 vs 146.7 ± 23.8; $P < 0.01$) than nonusers after adjustment for a large number of confounders, including age, weight, smoking, other medications, and prevalent diseases.

Conclusions: Use of statins was associated with better cortical bone characteristics in older women. (***J Clin Endocrinol Metab*** **104: 250–257, 2019)**

Osteoporosis is characterized by impaired bone microstructure and reduced bone strength, resulting in increased fracture risk (1–3). About 200 million people are estimated to be affected by osteoporosis, and around 8.9 million osteoporosis-related fractures occur every year globally (4, 5). In addition to low bone mineral density (BMD), several clinical risk factors contribute independently to fracture risk, including prior fracture, heredity, smoking, high alcohol consumption, oral glucocorticoid treatment, rheumatoid arthritis, and diseases that can lead to secondary osteoporosis (6–8). Osteoporotic fractures cause personal suffering in terms of

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Abbreviations: aBMD, areal bone mineral density; BMD, bone mineral density; BMI, body mass index; BV/TV, trabecular bone volume fraction; Ct.Ar, cortical area; Ct.Th, cortical thickness; Ct.vBMD, cortical volumetric bone mineral density; CV, coefficient of variation; HR-pQCT, high-resolution peripheral quantitative computed tomography; MCS, mental component score; PASE, Physical Activity Scale for the Elderly; PCS, physical component score; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; TUG, Timed Up and Go.

increased mortality and morbidity and lead to increase societal costs (9, 10).

The positive effects of the 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) on reducing cardiovascular risks have been well described (11, 12), and in recent years, evidence has emerged suggesting positive effects of statin treatment on bone health. Experimental studies indicate that statins can increase bone formation and inhibit bone resorption via reduced osteoclastogenesis (13). In a meta-analysis, statin use was associated with a higher BMD of the hip and spine in some, but not all, cross-sectional studies (14, 15). Due to the underlying condition, statin users differ from nonusers in terms of physical function, body mass index (BMI), stroke, and prevalence of diabetes, factors that are important for BMD (16). Therefore, discrepancies in associations between statin use and BMD could at least partly be due to a lack of appropriate adjustment for relevant confounders in the different studies. Furthermore, all previous studies used dual x-ray absorptiometry to measure BMD (17). Therefore, it is not known whether statin use is associated with increased trabecular or cortical volumetric BMD or bone size. In the current study, we investigated if statin treatment was associated with volumetric BMD and bone microstructure and if any observed difference was dependent on confounding factors, such as physical function, BMI, diabetes, or cardiovascular disease.

Materials and Methods

Subjects

Sahlgrenska University Hospital Prospective Evaluation of the Risk of Bone fracture (SUPERB) is a prospective, population-based study that was carried out in the greater Gothenburg area. The study comprises 3028 women who were 75 to 80 years old. Women were chosen randomly from the Swedish national population register. Initially, an invitation was sent by letter. At a later stage, the women were asked via telephone if they wanted to participate. The prerequisite for participation was to be physically mobile and able to understand instructions in Swedish. Additionally, it was required to have at least one hip that could be assessed for areal BMD (aBMD). The women who accepted and fulfilled the inclusion criteria were invited to undergo an examination at the Osteoporosis Research Clinic, Department of Geriatrics, Sahlgrenska University Hospital, Mölndal, Sweden. Before participating, all women signed an informed consent. The study protocol was approved by the ethical review board at the University of Gothenburg.

Anthropometrics and physical function tests

Standardized equipment was used to measure height and weight. Body height was assessed with two consecutive measurements, from which an average was calculated. If a difference of >5 mm was found, a third measurement was done, and the two most equal measurements were used. A 10-m walk test was used to measure walking speed (18). Participants were asked to walk 10 m twice at their chosen speed. The first 2 m and the last 2 m were used for acceleration and retardation, respectively; the middle 6 m were timed. The average of the two trials was used in the analyses. The 30-second chair-stand test was used to measure lower body strength (19). The participants were asked to rise up from a chair with their arms crossed over the chest. The number of repetitions over 30 seconds was recorded. Timed Up and Go (TUG) (20) is a test of mobility and balance in which the participants are timed during rising from a chair, walking 3 m, turning, walking back, and sitting down again. Balance was tested using the one leg standing test (21). The participants had a practice round, after which the test was performed twice for each leg. The best time for each leg was used to calculate an average. To assess grip strength (22), a Saehan hydraulic hand dynamometer was used (model SH5001; Saehan Corporation, Masan, South Korea). The participants were asked to hold their elbow at a 90° angle while resting the lower arm on a flat surface. Participants made two attempts with each hand. An average of four trials was used in the analyses.

Questionnaires

A standardized questionnaire including history of fractures, medical history, and current medication was used. The questionnaire included questions regarding physical activity, current smoking, alcohol consumption, parental history of hip fracture, incidence of falls in the past 12 months, calcium intake, and use of medication. The women were asked about their history of fractures after the age of 50, except for skull fractures, which were not included. A validated questionnaire was used to estimate dietary calcium intake. The calculation was based on food-derived intake and supplements (23). Another validated questionnaire, the Physical Activity Scale for the Elderly (PASE), was used to estimate physical activity for the last 7 days before the inclusion in the study (24). PASE provides a complete overview of the physical activity in persons 65 years and older by multiplying the number of hours in different activities per week or attendance (yes/no) by given weights. The participants' perception of their own health was evaluated by the SF-12 Health Survey. SF-12 includes components regarding physical health [physical component score (PCS)] and mental health [mental health component score (MCS)] (25, 26).

Dual-energy X-ray absorptiometry

A Hologic Discovery A device (Hologic, Waltham, MA) was used to measure aBMD at the femoral neck, total hip, and L1 to L4 of the lumbar spine as well as body composition from a total body scan. At our facility, the coefficients of variation (CVs) were 1.3% for femoral neck aBMD, 0.8% for total hip aBMD, 0.7% for lumbar spine aBMD, 1.1% for fat mass, and 0.6% for lean mass. Data were obtained from women of the same age.

High-resolution peripheral quantitative computed tomography

Bone microstructure and geometry were assessed in the nondominant arm (radius) and lower leg (tibia) of the corresponding side with high-resolution peripheral quantitative computed tomography (HR-pQCT) equipment (Xtreme CT; Scanco Medical AG, Brüttisellen, Switzerland). All measurement

procedures were performed in accordance with instructions and protocols from the manufacturer (27). The first image was derived at an ultradistal site 9.5 and 22.5 mm proximal to the reference line for radius and tibia, respectively. A more proximal measurement at 14% of the measured bone length from the end plate (distal site) was carried out to assess a bone site primarily composed of cortical bone (28). A three-dimensional construction of the bone was assembled using 110 slices obtained from each measurement. The nominal isotropic resolution was 82 μm. When all images had been processed (29), the following variables were available: trabecular bone volume fraction (BV/TV, %), trabecular thickness (Tb.Th, mm), trabecular separation (Tb.Sp, mm), trabecular number (Tb.N, per mm), cortical area (Ct.Ar, mm^2), cortical thickness (Ct.Th, mm), and cortical volumetric bone mineral density (Ct.vBMD, mg/cm^3). At the distal section, only cortical variables were analyzed. An image quality assessment was made with a grading from 1 to 5. A perfect quality was numbered as 1 and a suboptimal quality as 5. Regarding bone geometry and microstructure variables, only images with a quality level between 1 and 3 were used for analysis. Duplicate measurements in women between 75 and 80 years of age were used to calculate the CVs at the tibia (n = 6) and radius (n = 3). The CVs for the bone variables at the tibia ultradistal site were 0.8% for BV/TV, 1.9% for Tb.N, 2.6% for Tb.Th, 2.1% for Tb.Sp, 0.2% for Ct.Th, 0.2% for Ct.Ar, and 0.2% for Ct.vBMD. At the tibia distal site, the CVs were 0.4% for Ct.Ar, 0.3% for Ct.Th, and 0.2% for Ct.vBMD. At the ultradistal radius, the following CVs were obtained: 0.4% for BV/TV, 2.4% for Tb.N, 1.9% for Tb.Th, 2.4% for Tb.Sp, 1.2% for Ct.Th, 0.9% for Ct.Ar, and 0.4% for Ct.vBMD. At the radius distal site, the CVs were 0.1% for Ct.Ar, 0.3% for Ct.Th, and 0.1% for Ct.vBMD.

Cortical evaluation

An Image Processing Language (IPL v5.08b; Scanco Medical AG) was used to further process all images (30). To separate cortical bone from trabecular bone and to sequester the bone from extraosseal soft tissue, contours were placed automatically at both the periosteal and endosteal sides of the cortical bone. All contours were inspected for accuracy, and, if required, corrected manually. To calculate cortical porosity, the equation Cortical Pore Volume/(Cortical Pore Volume + Cortical Bone Volume) was used (30, 31). At the radius, the CV for cortical porosity was 5.3% at the ultradistal site and 13.3% at the distal site. The CV for cortical porosity was 0.9% in the tibia at the ultradistal site and 4.1% at the distal site (14% of bone length).

Statistical analyses

All statistical analyses were performed with SPSS Statistics Version 21 (IBM Corporation, Armonk, NY). The associations between statin use and physical function were calculated with linear regression, with adjustments for the covariates age, height, weight, MCS, prior stroke, myocardial infarction, angina pectoris, and diabetes. Linear regression was also used to examine the relationship between the use of statins and bone variables adjusted for the following covariates: age, height, weight, MCS, physical component summary, PCS, prior stroke, myocardial infarction, angina pectoris, diabetes, grip strength, oral glucocorticoid usage, rheumatoid arthritis, current smoking, heredity of hip fracture, previous fracture after the age of 50, and high alcohol intake (more than three standardized glasses of alcohol per day). Differences in bone variables according to group of statin use were tested using ANOVA with LSD *post hoc* test. Independent samples *t* test was used to investigate differences between groups regarding continuous variables. For dichotomous variables, χ^2 and Fisher exact test were chosen. Values are presented as mean ± SD for continuous variables and percentage, together with number of participants for dichotomous variables, unless stated otherwise. In analyses using linear regression models, standardized β values were presented. A P value <0.05 was considered significant. A subanalysis comparing bone traits between statin-treated women and matched control subjects was also performed. One control for every statin-treated woman was identified using RStudio (RStudio, Inc., Boston, MA) and the package MatchIt (32). The matching procedure was performed based on age, height, weight, diabetes, prior stroke, angina pectoris, myocardial infarction, PASE, PCS, and MCS.

Results

Cohort characteristics

In this population-based, cross-sectional study, 3028 women (age, 77.8 ± 1.6 years) were included. Of these, 803 were receiving treatment with statins. In the whole cohort, women with statin treatment were heavier; were less physically active; and had a higher prevalence of diabetes, prior stroke, myocardial infarction, and angina pectoris than women not receiving statins (Table 1). In a subanalysis, 799 statin users were compared with a matched control group of 799 nontreated women. After matching, small but significant differences in diabetes, stroke, and angina pectoris prevalence persisted between the groups (Table 1). In general, the groups were well balanced regarding age, height, weight, mental health, fall accidents in the previous year, hyperthyroidism, hypothyroidism, oral glucocorticoid use, myocardial infarction, Parkinson disease, rheumatoid arthritis, current smoking, prevalent fracture, heredity of hip fracture, chronic liver disease, and celiac disease (Table 1).

Physical function indices

In the complete cohort, several parameters of physical function, including grip strength, one leg standing, and TUG, were inferior in statin users compared with control subjects; however, except for TUG, these differences did not remain significant after adjusting for age, height, weight, mental health, prior stroke, myocardial infarction, angina pectoris, and diabetes (Table 2). Chair stand test was inferior in statin users compared with matched control subjects after statistical adjustments. No other variables estimating physical fitness differed significantly between the groups (Table 2).

aBMD

Statin users had higher BMD at the femoral neck, total hip, and lumbar spine in the whole cohort. After adjustment for covariates including age, height, weight, mental health, physical health, prior stroke, myocardial infarction, angina pectoris, diabetes, grip strength, oral glucocorticoid treatment,

Table 1. Characteristics of Older Women With and Without Statin Use

	Total Cohort			Matched Cohort		
	Statin No (n = 2221)	Statin Yes (n = 803)	*P* Value	Statin No (n = 799)	Statin Yes (n = 799)	*P* Value
Age, y	77.8 ± 1.6	77.8 ± 1.6	0.15	77.8 ± 1.6	77.9 ±0.1.6	0.65
Height, cm	161.9 ± 5.9	161.7 ± 5.8	0.38	161.6 ± 5.9	161.7 ± 5.8	0.87
Weight, kg	68.2 ± 12.1	70.3 ± 11.8	<0.001	71.2 ± 14.0	70.2 ± 11.8	0.14
Physical activity (PASE)	106 ± 51.4	99.6 ± 48.9	0.004	97.2 ± 49.9	99.6 ± 48.9	0.33
MCS	53.6 ± 9.3	53.3 ± 9.6	0.32	53.7 ± 9.3	53.2 ± 9.6	0.39
PCS	45.4 ± 10.9	44.3 ± 10.9	0.01	44.4 ± 11.1	44.3 ± 10.9	0.92
Fall accident last year, % (n)	29.2 (648)	30.8 (247)	0.40	30.9 (247)	30.5 (244)	0.87
Hyperthyroidism, % (n)	5.0 (111)	5.2 (42)	0.87	5.6 (45)	5.3 (42)	0.74
Hypothyroidism, % (n)	14.0 (310)	14.1 (113)	0.95	15.2 (121)	14.0 (112)	0.50
Diabetes, % (n)	5.9 (131)	20.4 (164)	<0.001	16.4 (131)	20.5 (164)	0.03
Oral glucocorticoids, % (n)	3.6 (81)	2.6 (21)	0.17	3.1 (25)	2.6 (21)	0.55
Parkinson disease, % (n)	0.7 (16)	1.1 (9)	0.36[a]	0.6 (5)	1.1 (9)	0.42[a]
Rheumatoid arthritis, % (n)	3.7 (83)	4.6 (37)	0.28	4.3 (34)	4.6 (37)	0.71
Prior stroke, % (n)	4.1 (90)	15.4 (124)	<0.001	11.3 (90)	15.5 (124)	0.01
Myocardial infarction, % (n)	2.8 (63)	10.1 (81)	<0.001	7.8 (62)	10.1 (81)	0.10
Angina pectoris, % (n)	3.0 (66)	12.2 (98)	<0.001	8.1 (65)	12.3 (98)	0.01
Current smoking, % (n)	5.1 (113)	5.5 (44)	0.67	5.8 (46)	5.5 (44)	0.83
Prevalent fracture, % (n)	37.2 (827)	35.5 (285)	0.38	37.2 (297)	35.4 (283)	0.47
Heredity of hip fracture, % (n)	17.8 (396)	15.6 (125)	0.15	19.3 (154)	15.6 (125)	0.06
High alcohol intake, % (n)	0.5 (12)	0.6 (5)	0.79[a]	0.4 (3)	0.6 (5)	0.73
Chronic liver disease, % (n)	0.6 (13)	0.1 (1)	0.13[a]	0.6 (5)	0.1 (1)	0.22
Celiac disease, % (n)	1.4 (31)	1.5 (12)	0.83	2.0 (16)	1.5 (12)	0.45

An independent samples *t* test was used to compare differences in continuous variables between statin users and nonusers. Proportions for dichotomous variables were compared by χ^2 test or Fisher exact test for small sample sizes. Propensity score matching was used to identify matched control subjects. High alcohol intake was defined as more than three standard glasses per d. A *P* value <0.05 was considered significant.

Abbreviations: MCS, mental health component score; PCS, physical health component score.

[a]Fisher exact test.

rheumatoid arthritis, current smoking, high alcohol consumption (more than three standard drinks per day), parental hip fracture, and previous fractures, only total hip BMD remained significantly higher in statin users (Table 3). There were no significant differences in BMD between statin users and matched control subjects (Table 3).

Bone geometry and microarchitecture

At the ultradistal site, there was a significant difference in several bone traits, in favor of statin users. Such differences were observed for trabecular bone volume fraction, trabecular number, cortical area, and Ct.vBMD. However, after adjustment for age, height, weight, MCS and PCS scores, prior stroke, myocardial infarction, angina pectoris, diabetes, grip strength, oral glucocorticoid treatment, rheumatoid arthritis, current smoking, high alcohol consumption (more than three standard drinks per day), parental hip fracture, and prevalent fracture, differences between statin users and nonusers were attenuated for most trabecular bone traits but remained significant for cortical area and Ct.vBMD at both the radius and tibia (Table 3). At the 14% sites of the radius and tibia, statin users had greater cortical area, lower

Table 2. Physical Function in Older Women Treated With Statins Compared With Control Subjects

	Complete Cohort					Matched Cohort				
Function	Statin No (n = 2204)	Statin Yes (n = 796)	*P* Value	β	Adjusted *P* Value	Statin No (n = 790)	Statin Yes (n = 792)	*P* Value	β	Adjusted *P* Value
One leg standing, s	14.2 ± 9.7	13.3 ± 9.3	0.05	0.01	0.71	12.54 ± 9.4	13.3 ± 9.3	0.16	0.05	0.09
Timed up and go, s	8.6 ± 3.1	9.0 ± 3.5	0.005	−0.04	0.02	9.1 ± 3.6	9.0 ± 3.5	0.52	−0.04	0.07
Chair stand test, number/30 s	11.3 ± 3.6	11.0 ± 3.3	0.05	0.03	0.09	10.8 ± 3.5	11.1 ± 3.3	0.14	0.06	0.01
Grip strength, kg	14.8 ± 5.5	14.4 ± 5.5	0.04	0.001	0.95	14.6 ± 5.4	14.4 ± 5.5	0.47	−0.005	0.85

An independent samples *t* test was used to compare differences in indices of physical function between statin users and nonusers. Differences in these parameters were also investigated in linear regression models, adjusted for age, height, weight, mental health (MCS), prior stroke, myocardial infarction, angina pectoris, and diabetes for the complete cohort and prior stroke, myocardial infarction, angina pectoris, and diabetes for the matched cohort. Results for the linear regressions are presented as standardized β. A *P* value <0.05 was considered significant. Propensity score matching was used to identify matched control subjects.

Table 3. Areal Bone Mineral Density, Bone Geometry, and Microstructure in Older Women With and Without Statin Treatment

	Complete Cohort					Matched Cohort				
	Statin No (n = 2210)	Statin Yes (n = 801)	*P* Value	β	Adjusted *P* Value	Statin No (n = 797)	Statin Yes (n = 797)	*P* Value	β	Adjusted *P* Value
Dual x-ray absorptiometry										
Femoral neck aBMD, g/cm^2	0.66 ± 0.11	0.67 ± 0.11	0.03	0.02	0.18	0.66 ± 0.11	0.67 ± 0.11	0.13	0.03	0.27
Hip total aBMD, g/cm^2	0.80 ± 0.12	0.81 ± 0.12	0.003	0.04	0.03	0.80 ± 0.12	0.81 ± 0.12	0.06	0.04	0.11
Lumbar spine aBMD, g/cm^2	0.94 ± 0.17	0.96 ± 0.16	0.01	0.01	0.73	0.95 ± 0.18	0.96 ± 0.16	0.80	−0.01	0.67
HR-pQCT										
Tibia ultradistal	(n = 2147)	(n = 777)				(n = 777)	(n = 773)			
Trabecular bone volume fraction, %	12.1 ± 3.0	12.4 ± 2.8	0.01	0.03	0.14	12.2 ± 3.0	12.4 ± 2.8	0.08	0.04	0.14
Trabecular thickness, μm	68.7 ± 12.8	69.0 ± 12.7	0.51	0.01	0.49	67.9 ± 12.2	69.0 ± 12.7	0.08	0.04	0.09
Trabecular number per mm	1.77 ± 0.36	1.81 ± 0.34	0.01	0.02	0.23	1.80 ± 0.37	1.81 ± 0.34	0.49	0.01	0.74
Cortical area, mm^2	77.1 ± 22.9	80.9 ± 24.1	<0.001	0.06	<0.001	77.6 ± 24.0	80.9 ± 24.2	0.01	0.07	0.003
Cortical volumetric BMD, mg/cm^3	737 ± 67.5	744 ± 73.1	0.01	0.05	0.01	736 ± 71.3	744 ± 73.2	0.02	0.07	0.01
Cortical porosity, %	12.4 ± 4.0	12.1 ± 3.9	0.05	−0.05	0.02	12.4 ± 4.0	12.1 ± 3.9	0.13	−0.05	0.05
Tibia distal (14% of bone length)	(n = 2181)	(n = 792)				(n = 785)	(n= 7 88)			
Cortical area, mm^2	146.7 ± 23.8	150.0 ± 23.6	0.001	0.05	0.01	147.7 ± 24.8	149.9 ± 23.7	0.06	0.05	0.05
Cortical volumetric BMD, mg/cm^3	914 ± 41.5	919 ± 42.6	0.002	0.06	0.005	914 ± 41.0	919 ± 42.6	0.01	0.07	0.006
Cortical porosity, %	5.4 ± 2.5	5.2 ± 2.4	0.01	−0.06	0.01	5.5 ± 2.6	5.2 ± 2.4	0.02	−0.07	0.01
Radius ultradistal	(n = 1792)	(n = 650)				(n = 643)	(n = 648)			
Trabecular bone volume fraction, %	9.9 ± 3.5	10.4 ± 3.3	0.01	0.04	0.09	10.0 ± 3.5	10.4 ± 3.3	0.19	0.05	0.05
Trabecular thickness, μm	57.8 ± 11.2	59.0 ± 11.3	0.02	0.05	0.03	57.4 ± 10.7	59.0 ± 11.3	0.01	0.08	0.004
Trabecular number per mm	1.70 ± 0.44	1.75 ± 0.42	0.01	0.03	0.17	1.72 ± 0.44	1.75 ± 0.42	0.16	0.03	0.23
Cortical area, mm^2	36.9 ± 11.4	39.1 ± 11.7	<0.001	0.07	0.002	37.9 ± 11.8	39.1 ± 11.7	0.07	0.05	0.06
Cortical volumetric BMD, mg/cm^3	766 ± 78.3	779 ± 80.3	<0.001	0.06	0.01	771 ± 79.5	779 ± 80.3	0.07	0.06	0.05
Cortical porosity, %	4.4 ± 2.2	4.6 ± 2.3	0.17	−0.06	0.01	4.5 ± 2.3	4.6 ± 2.3	0.46	−0.04	0.20
Radius distal (14% of bone length)	(n = 2041)	(n = 737)				(n = 743)	(n = 734)			
Cortical area, mm^2	58.6 ± 9.7	60.5 ± 9.6	<0.001	0.06	0.001	59.6 ± 9.7	60.5 ± 9.6	0.07	0.04	0.13
Cortical volumetric BMD, mg/cm^3	1001 ± 38.4	1008 ± 39.1	<0.001	0.08	<0.001	1002 ± 39.3	1008 ± 39.1	0.01	0.08	0.002
Cortical porosity, %	2.5 ± 2.0	2.2 ± 1.9	0.01	−0.07	0.001	2.4 ± 2.0	2.2 ± 1.9	0.12	−0.06	0.03

An independent samples *t* test was used to compare differences in indices of bone parameters between statin users and nonusers for the complete cohort and the matched individuals. Differences in these parameters were also investigated in linear regression models, where the total cohort analysis was adjusted for age, height, weight, mental health (MCS), physical health (PCS), prior stroke, myocardial infarction, angina pectoris, diabetes, grip strength, oral glucocorticoid treatment, rheumatoid arthritis, current smoking, high alcohol consumption (more than three standard drinks per d), parental hip fracture, and prevalent fracture. The matched analysis was adjusted for prior stroke, myocardial infarction, angina pectoris, diabetes, grip strength, oral glucocorticoid treatment, rheumatoid arthritis, current smoking, high alcohol consumption (more than three standard drinks per d), parental hip fracture, and prevalent fracture. Results for the linear regressions are presented as standardized β. A *P* value <0.05 was considered significant. Distal refers to HR-pQCT measurements at 14% of tibia bone length; Ultradistal refers to HR-pQCT measurements according to the manufacturer. Propensity score matching was used to identify matched control subjects.

cortical porosity, and higher Ct.vBMD than matched control subjects after adjustment for confounders (Table 3).

Cortical bone variables in women with different types of statins and in matched control subjects

In the whole cohort, 551 subjects were treated with simvastatin, and 239 subjects were treated with atorvastatin (n = 201) or rosuvastatin (n = 28). Cortical bone parameters were compared between these subgroups of statin users and 798 matched control subjects. Women with atorvastatin or rosuvastatin had higher Ct.vBMD in both the radius and tibia. A nonsignificant trend toward lower cortical porosity at the tibia was seen for women with atorvastatin or rosuvastatin compared with simvastatin (Fig. 1). Simvastatin users had higher Ct.vBMD than control subjects at the tibia.

Discussion

In the current study, we found that women with ongoing statin treatment had lower cortical porosity, higher Ct.vBMD, and greater cortical area than control subjects, indicating that the main effect on bone of this treatment could be on the cortical bone. We also found that statin use was associated with a higher dual x-ray absorptiometry–derived BMD at the femoral neck, total hip, and lumbar spine, but these differences only remained for the hip with relatively more cortical bone than the spine after adjustments for confounders and could not be detected at all when comparing statin users with matched control subjects. Differences in physical function, diabetes, cardiovascular disease (stroke, previous myocardial infarction, and angina pectoris) prevalence, and BMI between statin-treated women and untreated women were substantial and likely affected the observed unadjusted associations. When taking these differences into account by statistical adjustment or by using matched control subjects, differences in aBMD diminished or vanished, which could explain some of the discrepancies in the earlier studies regarding statin use and aBMD (14, 15).

Experimental studies have demonstrated that statins stimulate bone formation in cultured osteoblasts, increase trabecular bone volume in rats, and augment calvarial thickening in mice (33). Statins have been considered to impair osteoclastic differentiation and activity as well

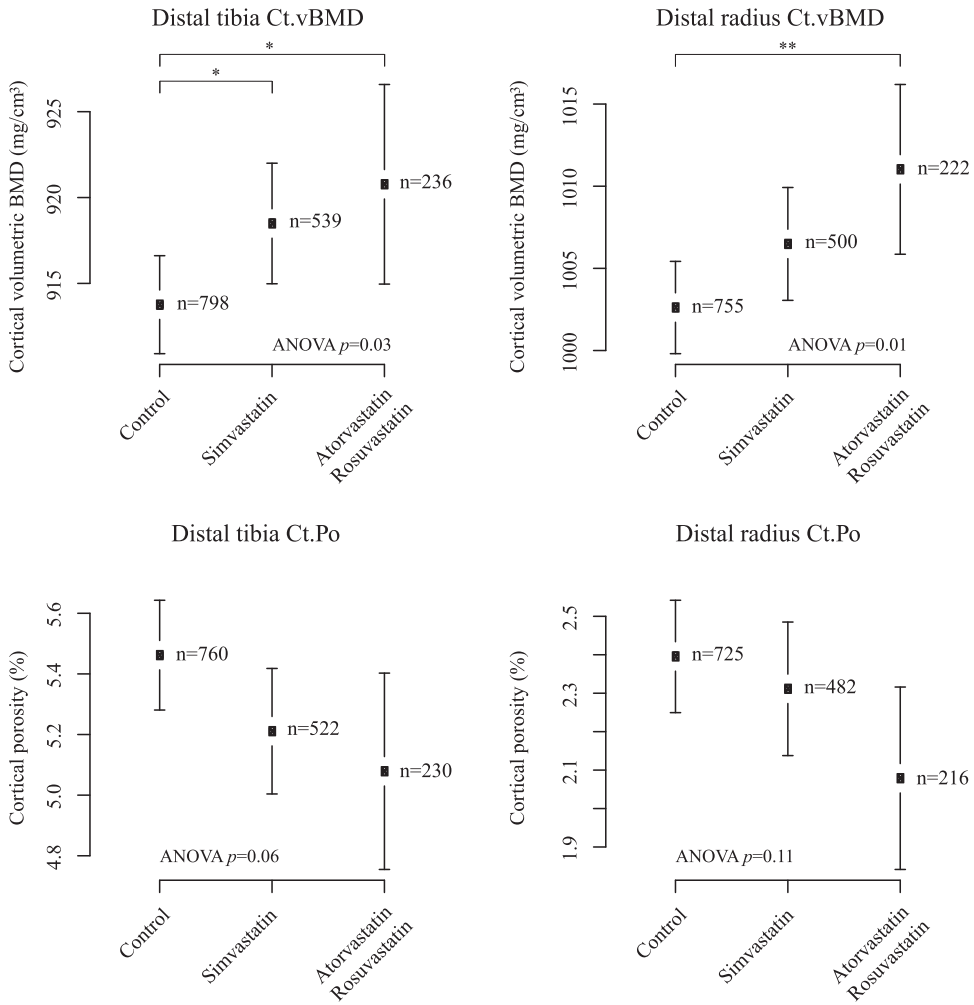

Figure 1. Group-to-group differences were investigated using ANOVA followed by LSD *post hoc* test. For Ct.vBMD at the tibia, 199 subjects had atorvastatin and 37 had rosuvastatin (n = 236). For Ct.Po at the tibia, 194 subjects had atorvastatin and 36 had rosuvastatin (n = 230). For Ct.vBMD at the radius, 189 subjects had atorvastatin and 33 had rosuvastatin (n = 222). For Ct.Po at the radius, 184 subjects had atorvastatin and 32 had rosuvastatin (n = 216). $*P < 0.05$; $**P < 0.01$.

(34, 35). Thus, data from experimental studies indicate that statins stimulate bone formation and reduce bone resorption. In the current study, similar associations between statin use and cortical bone parameters were observed for both the radius and tibia, indicating a systemic effect on cortical bone and that any statin-mediated effect is independent on weight-induced loading on the bone. The mechanism of action mediating the statin effect on bone is not clear but may involve a direct effect on bone cells or a general anti-inflammatory or vascular effect (34, 35).

In a randomized, placebo-controlled trial investigating the effect of simvastatin on BMD in postmenopausal women, statin treatment did not increase BMD at the spine or hip, but a significant increase was seen in the forearm, a bone site consisting primarily of cortical bone (36). In a smaller randomized trial of 64 older men (mean age, 80 years), treatment with atorvastatin increased BMD at the total hip but not at the femoral neck or lumbar spine (37). Thus, limited data from small randomized controlled trials suggest a small effect of statins on BMD on selected sites. In the current study, we observed a slightly higher BMD at the total hip in statin users than in nonusers, a difference that remained significant in the whole cohort. This difference was not significant when comparing statin users with matched control subjects, although of the same magnitude as that observed in the whole cohort, indicating that low statistical power could explain the lack of significance.

The reported data from cohort studies is somewhat divergent. A recent meta-analysis including 23 observational studies concluded that statin use was associated with higher BMD at the total hip and lumbar spine, improved bone turnover markers, and lower fracture risk. The differences appeared to be larger for men than for women (17). Differences in the ability to take confounders, such as BMI and diabetes prevalence between statin users and nonusers, could contribute to the

conflicting results. In the large Women Health Initiative study, statin users had somewhat higher age and BMI-adjusted total hip BMD than nonusers, but this association was lost after multivariate adjustment (38), in line with the findings of the current study.

A limitation of this study is that we had no access to information on doses of statins or to duration of treatment. This information is important because studies have demonstrated that patients with longer statin treatment have a more favorable bone metabolism (39, 40). Although we compared statin users with matched control subjects, some imbalances, including a larger prevalence of diabetes, stroke, and angina pectoris in statin users than in control subjects, remained. These imbalances could have affected the observed associations. The studied cohort only includes older women within a narrow age span, which limits generalizability to other populations. The study also has strengths. It is a large population-based study with detailed information on possible confounders, allowing for proper statistical adjustments and selection of appropriate control groups in the analysis. We found that statin users had signs of inferior physical function but higher BMD than nonusers, but some of these associations (one leg standing and grip strength) were lost or attenuated after appropriate statistical adjustment or by using a well-matched control group. The slightly better cortical bone microstructure in statins users vs nonusers is unlikely to be explained by differences in physical function, which indicates that statins have an effect on the cortical bone.

This study reports associations between statin use and bone microstructure, volumetric BMD, and bone geometry. We were also able to study associations between statin use according to potency of statin medication. The more potent statins, atorvastatin and rusovastatin, were associated with the best cortical bone parameters.

In summary, our findings demonstrate that statin use is associated with better cortical bone characteristics and that these associations were dependent on statin potency. Larger randomized trials are necessary to determine if statins can enhance cortical bone geometry and Ct.vBMD and reduce cortical porosity.

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Correspondence and Reprint Requests: Mattias Lorentzon, PhD, Geriatric Medicine, Institute of Medicine, Sahlgrenska University Hospital/Mölndal, Building K, 6th floor, SE-431 80 Mölndal, Sweden. E-mail: mattias.lorentzon@medic.gu.se.

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References

1. Riggs BL, Melton LJ III. The worldwide problem of osteoporosis: insights afforded by epidemiology. *Bone*. 1995;**17**(5, Suppl)505S–511S.
2. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. *Indian J Orthop*. 2011;**45**(1):15–22.
3. Walker-Bone K, Walter G, Cooper C. Recent developments in the epidemiology of osteoporosis. *Curr Opin Rheumatol*. 2002;**14**(4):411–415.
4. Pisani P, Renna MD, Conversano F, Casciaro E, Di Paola M, Quarta E, Muratore M, Casciaro S. Major osteoporotic fragility fractures: risk factor updates and societal impact. *World J Orthop*. 2016;**7**(3):171–181.
5. Lin X, Xiong D, Peng YQ, Sheng ZF, Wu XY, Wu XP, Wu F, Yuan LQ, Liao EY. Epidemiology and management of osteoporosis in the People's Republic of China: current perspectives. *Clin Interv Aging*. 2015;**10**:1017–1033.
6. Lorentzon M, Cummings SR. Osteoporosis: the evolution of a diagnosis. *J Intern Med*. 2015;**277**(6):650–661.
7. Kanis JA, McCloskey EV, Johansson H, Oden A, Strom O, Borgstrom F. Development and use of FRAX in osteoporosis. *Osteopros Int*. 2010;**21**(Suppl 2):S407–S413.
8. Silverman SL, Komm BS, Mirkin S. Use of FRAX®-based fracture risk assessments to identify patients who will benefit from osteoporosis therapy. *Maturitas*. 2014;**79**(3):241–247.
9. Dempster DW. Osteoporosis and the burden of osteoporosis-related fractures. *Am J Manag Care*. 2011;**17**(Suppl 6):S164–S169.
10. Rousculp MD, Long SR, Wang S, Schoenfeld MJ, Meadows ES. Economic burden of osteoporosis-related fractures in Medicaid. *Value Health*. 2007;**10**(2):144–152.
11. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for prevention of cardiovascular disease in adults: evidence report and systematic review for the US Preventive Services Task Force. *JAMA*. 2016;**316**(19):2008–2024.
12. Rauch U, Osende JI, Chesebro JH, Fuster V, Vorchheimer DA, Harris K, Harris P, Sandler DA, Fallon JT, Jayaraman S, Badimon JJ. Statins and cardiovascular diseases: the multiple effects of lipid-lowering therapy by statins. *Atherosclerosis*. 2000;**153**(1):181–189.
13. Ruan F, Zheng Q, Wang J. Mechanisms of bone anabolism regulated by statins. *Biosci Rep*. 2012;**32**(6):511–519.
14. Uzzan B, Cohen R, Nicolas P, Cucherat M, Perret GY. Effects of statins on bone mineral density: a meta-analysis of clinical studies. *Bone*. 2007;**40**(6):1581–1587.
15. Liu J, Zhu LP, Yang XL, Huang HL, Ye DQ. HMG-CoA reductase inhibitors (statins) and bone mineral density: a meta-analysis. *Bone*. 2013;**54**(1):151–156.
16. Lee DS, Markwardt S, Goeres L, Lee CG, Eckstrom E, Williams C, Fu R, Orwoll E, Cawthon PM, Stefanick ML, Mackey D, Bauer DC, Nielson CM. Statins and physical activity in older men: the osteoporotic fractures in men study. *JAMA Intern Med*. 2014;**174**(8):1263–1270.
17. An T, Hao J, Sun S, Li R, Yang M, Cheng G, Zou M. Efficacy of statins for osteoporosis: a systematic review and meta-analysis. *Osteopor Int*. 2017;**28**(1):47–57.
18. Bohannon RW. Comfortable and maximum walking speed of adults aged 20-79 years: reference values and determinants. *Age Ageing*. 1997;**26**(1):15–19.

19. Jones CJ, Rikli RE, Beam WCA. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport*. 1999;**70**(2):113–119.
20. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;**39**(2):142–148.
21. Giorgetti MM, Harris BA, Jette A. Reliability of clinical balance outcome measures in the elderly. *Physiother Res Int*. 1998;**3**(4):274–283.
22. Martins JC, Aguiar LT, Lara EM, Teixeira-Salmela LF, Faria CD. Assessment of grip strength with the modified sphygmomanometer test: association between upper limb global strength and motor function. *Braz J Phys Ther*. 2015;**19**(6):498–506.
23. Angbratt M, Möller M. Questionnaire about calcium intake: can we trust the answers? *Osteoporos Int*. 1999;**9**(3):220–225.
24. Washburn RA, McAuley E, Katula J, Mihalko SL, Boileau RA. The physical activity scale for the elderly (PASE): evidence for validity. *J Clin Epidemiol*. 1999;**52**(7):643–651.
25. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Leplege A, Prieto L, Sullivan M. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA Project. International Quality of Life Assessment. *J Clin Epidemiol*. 1998;**51**(11):1171–1178.
26. Huo T, Guo Y, Shenkman E, Muller K. Assessing the reliability of the short form 12 (SF-12) health survey in adults with mental health conditions: a report from the wellness incentive and navigation (WIN) study. *Health Qual Life Outcomes*. 2018;**16**(1):34.
27. MacNeil JA, Boyd SK. Improved reproducibility of high-resolution peripheral quantitative computed tomography for measurement of bone quality. *Med Eng Phys*. 2008;**30**(6):792–799.
28. Nilsson M, Sundh D, Mellström D, Lorentzon M. Current physical activity is independently associated with cortical bone size and bone strength in elderly Swedish women. *J Bone Miner Res*. 2017;**32**(3):473–485.
29. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. *Technol Health Care*. 1998;**6**(5-6):329–337.
30. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. *Bone*. 2010;**47**(3):519–528.
31. Sundh D, Rudäng R, Zoulakis M, Nilsson AG, Darelid A, Lorentzon M. A high amount of local adipose tissue is associated with high cortical porosity and low bone material strength in older women. *J Bone Miner Res*. 2016;**31**(4):749–757.
32. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw*. 2011;**42**(8).
33. Mundy G, Garrett R, Harris S, Chan J, Chen D, Rossini G, Boyce B, Zhao M, Gutierrez G. Stimulation of bone formation in vitro and in rodents by statins. *Science*. 1999;**286**(5446):1946–1949.
34. Tsartsalis AN, Dokos C, Kaiafa GD, Tsartsalis DN, Kattamis A, Hatzitolios AI, Savopoulos CG. Statins, bone formation and osteoporosis: hope or hype? *Hormones (Athens)*. 2012;**11**(2):126–139.
35. Oryan A, Kamali A, Moshiri A. Potential mechanisms and applications of statins on osteogenesis: Current modalities, conflicts and future directions. *J Control Release*. 2015;**215**:12–24.
36. Rejnmark L, Buus NH, Vestergaard P, Heickendorff L, Andreasen F, Larsen ML, Mosekilde L. Effects of simvastatin on bone turnover and BMD: a 1-year randomized controlled trial in postmenopausal osteopenic women. *J Bone Miner Res*. 2004;**19**(5):737–744.
37. Chen ZG, Cai HJ, Jin X, Lu JH, Wang J, Fang NY. Effects of atorvastatin on bone mineral density (BMD) and bone metabolism in elderly males with osteopenia and mild dyslipidemia: a 1-year randomized trial. *Arch Gerontol Geriatr*. 2014;**59**(3):515–521.
38. LaCroix AZ, Cauley JA, Pettinger M, Hsia J, Bauer DC, McGowan J, Chen Z, Lewis CE, McNeeley SG, Passaro MD, Jackson RD. Statin use, clinical fracture, and bone density in postmenopausal women: results from the Women's Health Initiative Observational Study. *Ann Intern Med*. 2003;**139**(2):97–104.
39. Cvijanovic O, Bicanic N, Orlic ZC, Majanovic SK, Wensveen TT, Bubic I. Effect of statin therapy duration on bone turnover markers in dyslipidemic patients. *Period Biol*. 2015;**117**(1):73–79.
40. Lin TK, Chou P, Lin CH, Hung YJ, Jong GP. Long-term effect of statins on the risk of new-onset osteoporosis: a nationwide population-based cohort study. *PLoS One*. 2018;**13**(5):e0196713.