Title:

Bisphosphonates intake and its Association with Changes of Periarticular Bone Area and Three-Dimensional Shape: Data from the Osteoarthritis Initiative (OAI)

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Abstract

Objective: To determine the association between bisphosphonate treatment with the change of periarticular bone area and three-dimensional (3D) shape in participants of the Osteoarthritis Initiative (OAI) study.

Design: Using propensity score (PS) matching method in female subjects, 48 bisphosphonate users and 105 non-users, who were matched for OA and osteoporosis related factors were included. Baseline and 24-month MRI-based bone area and 3D shape measurements were used. The association between bisphosphonate intake and 24-month interval changes of the periarticular bone area and 3D shape were evaluated using paired Wlcoxon signed rank test. We used conditional logistic regression models for determining the association between bisphosphonate intake and periarticular bone change, defined using the standard deviation of difference (SDD) and reliable change index (RCI) methods. P-valves have been adjusted for multiple comparisons using Benjamini & Hochberg procedure and false discovery rate (FDR) – adjusted p-values were reported.

Results: The 24-month interval increases in the periarticular bone area in medial side of tibia were significantly greater in non-users than users (FDR-adjusted p-value: 0.002). There was an approaching significance trend for lower medial tibial periarticular bone area expansion in bisphosphonates users in comparison with non-users (For 1SDD change, odds ratio 95% confidence interval (OR (95% CI)): 0.514 (0.271 – 0.975), FDR-adjusted p-value: 0.085) (for 1.96RCI change, OR (95% CI): 0.552 (0.309-0.986), FDR-adjusted p-value:0.085).

Conclusions: Bisphosphonate intake was associated with the reduced in the odds (approaching but not achieving significance) of expansion of periarticular bone area, specifically in the medial tibial sub-region.

Keywords: Bisphosphonates; Periarticular Bone; Osteoarthritis; 3T MRI; Knee

Running headline: Bisphosphonates & Periarticular Bone

Introduction

Bisphosphonates are traditionally used for the treatment of osteoporosis (OP). Recent studies have demonstrated a possible role of bisphosphonates in the treatment of osteoarthritis (OA) [1, 2]. The protective effects of bisphosphonates on OA-related structural damage including joint space loss and benefits for knee pain have been reported in a limited number of clinical studies [1]. It has also been demonstrated that there was a trend of lower radiographic OA progression in bisphosphonate users when compared with non-users in a study conducted on Osteoarthritis Initiative (OAI) cohort [3].

Despite these promising findings, the mechanisms by which bisphosphonates may induce protective effects on knee OA has not been entirely understood. It has been suggested that bisphosphonates may target the periarticular bone, which plays a pivotal role in the pathogenesis of OA and has been introduced as a biomarker of OA progression [4]. By inhibiting osteoclastic bone resorption and cellular secretion of transforming growth factor-β and matrix metalloproteinases, which are responsible for the cleavage of type II collagen; bisphosphonates may reduce periarticular bone turnover and lead to the local preservation of bone strength and microarchitecture, and eventually minimize OA progression [2, 5].

In our study, we aimed to evaluate whether bisphosphonate intake is associated with knee periarticular bone area and 3D shape changes during 24-months follow-up using a validated quantitative MRI-based analysis of periarticular bone.

Method

Study population:

We used the publicly available datasets of the OAI, which is an ongoing prospective observational study of 4,796 participants (additional details: https://oai.epi-ucsf.org). Our study used data from the Foundation for the National Institute of Health (FNIH) OA Biomarkers Consortium study, which is a nested case–control study within the OAI and comprised of 600 participants. In FNIH project, eligible participants had at least one knee with Kellgren-Lawrence (KL) grade of 1-3 at baseline and had available knee radiograph and 3T MRI at baseline and 24-months. Participants with knee/hip replacement or metal implants were excluded. Knees with advanced radiographic OA or severe symptoms at baseline were also excluded (minimum medial joint space with of <1.0mm and/or Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain score of >91.) Index knees were selected based on radiographic and pain progression in each participant (additional details: https://oai.epi-ucsf.org/datarelease/docs/FNIH). As most of the bisphosphonates users were female (93.3% of users), only females (n=353) were included (247 men were excluded). We used clinical data and MRI-based measurements from the baseline and 24-month time points. The study has received ethics board approval by the institutional review board at the University of California, San Francisco (Approval Number: 1000532) and all participants gave informed consent.

Exposure: Bisphosphonate intake

Bisphosphonate intake was evaluated using baseline self-reports. Participants were asked: "In the past five years, have you taken a bisphosphonate medication to treat OP or Paget's disease?" Patients who replied "yes" were considered to have a positive history. Other baseline variables related to bisphosphonates intake, including number of years treated and type of bisphosphonates used were also recorded.

Propensity score matching

In order to address confounding bias by indication for bisphosphonate intake, the propensity score (PS) matching method was used [6]. The study groups were matched for confounding baseline variables

(OA and OP-related factors) as follows: for OA - baseline age, BMI (Body mass index), WOMAC pain score, and KL grade; and for OP (defined by WHO fracture risk assessment tool, FRAX v3.11) - alcohol use (in the past 12 months), smoking status (current and past smoking), history of any bone fracture after 45 years old, history of hip fracture, history of vertebral/spine fracture, history of oral corticosteroid medications.

The nearest neighbor matching method with parallel matched sets was using variable ratio was used[6]. The 1:1/2/3 (based on the available data and caliper) with a caliper distance of 0.1 were used. For every bisphosphonate user, maximum number of best-matched non-user(s) was selected according to mentioned confounding variables [6]. Best matches were defined as participants with the highest-level match on their PS, which was calculated using logistic regression[6]. Out of the total 600 participants, 353 of them were female, and 351 of them had an available history of bisphosphonates intake. By considering matching method and available data, 48 bisphosphonates and 105 non-users were selected (Supplementary Fig. 1). For 8 bisphosphonate users no matched non-user was found using the matching method, due to the noticeable differences in baseline characteristics between study groups.

MRI acquisition and assessment: Periarticular bone area and 3D shape

MRI acquisition was performed using 3T MRI systems (Trio, Siemens Healthcare, Erlangen, Germany) located in four OAI centers at Baltimore, Columbus, Pawtucket, and Pittsburgh. The MRI pulse sequence protocol parameters were shown in Supplementary Table 1.

Periarticular bone morphology was automatically quantified by a computer-based method (iMorphics, Manchester, UK) using 3D Sagittal dual echo at steady state DESS sequences. Femur, tibia, and patella bone surfaces were automatically segmented from 3T DESS- water-excitation (WE) images using active appearance models provided by iMorphics [7]. The following variables were calculated: Total area of periarticular bone in mm^2 for 9 anatomical sub-regions including medial/lateral femoral condyle, medial/lateral tibial plateau, medial/lateral facet of patella, medial/lateral trochlea, lateral trochlea, and

femoral notch. Three vectors of periarticular 3D shape (femur, tibia, and patella) in normalized units where +1 is mean shape of OA knees and -1 is mean shape of non-OA knees were reported.

Change in periarticular bone area and 3D shape

The 24-months interval changes in the periarticular bone area (increasing/ expansion) and 3D shape (worsening) were defined based on standard deviation of difference (SDD) and reliable change index (RCI) methods. These methods allow accounting for the adverse effect of measurement errors on test interpretation.

A) Expansion or worsening change was defined for each sub-region that had a more than 1 SDD change. B) The RCI, as an established method for investigating the change of quantitative metrics, was used [8]. The RCI method was defined as ($\left| \text{X2-X1} \right| / \sqrt{2 \times \text{SE} \times \text{SE}}$), where X1 and X2 were the baseline and 24-month measurements, and SE was the standard error of baseline measurements. Any RCI that was ≥1.96 (95% confidence interval (CI)) was considered as expansion or worsening changes.

Statistical analysis

Baseline characteristics of the study populations were compared using t-test, (normally distributed continuous variables), non-parametric Mann-Whitney U test (non-normally distributed continuous variables), and Chi-Square test (categorical variables). The Kolmogorov-Smirnov and Shapiro-Wilk normality tests were performed to evaluate the distribution of data. The 24-months changes in the periarticular bone measurements which were non-normally distributed variable were compared between bisphosphonates user and non-user paired Wilcoxon signed rank test [9]. Next, the association between the bisphosphonate intake and periarticular bone change (more than 1SDD or 1.96RCI) was assessed using conditional logistic regression models, which is the preferred logistic model in the case of matched participants [10]. All the p-values were adjusted for multiple comparisosn by Benjamini-Hotchberg procedure and false discovery reate (FDR)-adjusted p-values were reported [11]. An FDR-adjusted p-value

of 0.05 and 0.10 was considered as the significance and approached-significance thresholds, respectively. Analyses were performed using SPSS (v.24, Chicago, IL) and R platform (v.2.15.1).

Results

A total number of 153 matched females (one index knee in each participant) with a baseline positive (n= 48) or negative (n= 105) history of bisphosphonates intake were included. In bisphosphonates users, the mean years of bisphosphonate intake was 3.6 years (range: 6months–18years); 83.3%, 14.6%, 2.1% of users were taking alendronate, risedronate, and other types, respectively. In baseline comparisons, there was no significant difference between the study groups (all p-value> 0.05; Table 1).

Table 1 positioned here

No significant difference was observed for the baseline periarticular bone measures between the study groups, except for medial tibial and sub-region which showed approached statistically significant difference (Supplementary Table 2). Paired Wilcoxon signed rank test revealed significant differences between bisphosphonates user versus non-user groups for 24-month change of periarticular areas in medial tibia (p-value: 0.003), lateral tibia (p-value 0.019), and lateral patella (p-value: 0.032) (Supplementary Table 3). However, only change of periarticular bone area in medial tibia sub-region remains statistically significant after p-value adjustment for mutliple comparisions (FDR-adjusted p-value:0.002). Change of periarticular 3D shape was not significantly different in bisphosphonate users when comapered to non-users (Supplementary Table 4).

Conditional logistic regression showed a trend of lower odds ratio (approached statistically significant) of medial tibia periarticular bone area expansion in bisphosphonates users (OR(95%CI): 0.514(0.271-0.975), FDR-adjusted p-value 0.085) (For 1.96RCI, OR(95%CI): 0.552(0.309–0.986), FDR-adjusted p-value 0.085) (Table 2). Although there were trends of associations (between bisphosphonate use

and periarticular bone area expansion/3D shape worsening), no statistically significant relationship was observed for other sub-regions (Table 2; and Supplementary Table 5).

(Table 2 positioned here)

Discussion

In this exploratory study, we found that positive history of bisphosphonate treatment showed an approach statistically significant association with the reduced periarticular bone area expansion in the medial tibial sub-region over 24-month.

Periarticular bone has been introduced as a potential biomarker that predicts worsening of structural damage and symptoms of knee OA [4]. It has been suggested that the expansion of periarticular area may play an initial role in the pathophysiology of knee OA[12]. In this regard, Hunter et al. investigated the role of the periarticular bone area and 3D shape (measured using iMorphics method) in predicting the clinically relevant OA progression in a study conducted on FNIH project [7]. They demonstrated that periarticular bone change, more than the 1SDD increase between 0-24months, in all knee joint anatomical sub-regions were associated with the future joint space loss and knee pain progression [7].

Regarding the mechanisms by which bisphosphonates may have beneficial effects on OA progression, it has been suggested that these drugs might lead to local improvement in periarticular bone strength through reducing bone turnover, which would improve load absorbance; and therefore, reduce the biomechanical stress on the overlying cartilage and subsequently reduce cartilage breakdown [2, 5]. This hypothesis has been primarily evaluated in a few clinical studies that showed a diminished periarticular trabecular bone loss in bisphosphonates users [13]. It has been shown that receiving risedronate for 24-months leads to an increase in periarticular vertical trabecular number in the fractal signature analysis [14]. Laslett et al. have demonstrated that bisphosphonates reduce the size of knee OA bone marrow lesions in 12-months follow-up clinical trial [15]. In line with animal studies and the limited previous clinical

observations, our results support a beneficial effect of bisphosphonate on reducing rates of periarticular bone expansion.

The current knowledge about the protective effect of bisphosphonates on the natural history of OA is also limited to a few numbers of clinical studies with inconsistent results [1]. In this regard, Laslett et al. have demonstrated that bisphosphonate intake was associated with the reduced knee pain scores in a study of 323 subjects (including 55 bisphosphonate users) from OAI dataset with 5-years follow-up [3]. A trend to less radiographic joint space narrowing was observed in bisphosphonate users when compared with non-users [3].

Our exploratory study has several limitations; this study was only limited to 153 knees and 24 months follow-up. Our included sample size and short-term follow up may not have been adequate for detection of MR-based periarticular changes. Also, the sample size calculation was not performed at this brief report was an exploratory analysis using the available FNIH dataset. Bisphosphonates intake was only defined based on baseline self-reports, and users have a wide range of usage (6 months to 18 years). Due to the small sample size and heterogeneous history of bisphospnate consumption, it was not possible to analyze the effect of duration and/or dosage of bisphosphante use on MR-based measurements. Therefore, the association between the bisphosphonate treatment and long-term periarticular bone changes needs to be further explored in larger studies. The potential effect of bisphosphonates on knee symptoms and radiographic progression was not evaluated, since these analyses have been previously reported in another study performed on OAI dataset [3]. There was an issue of confounding by indication bias, as several studies demonstrated that the OP and OA have an inverse relationship. In this regard, the study groups were completely matched for OA/OP-related factors. However, we did not investigate the role of bone mineral density, as the data was not available in OAI

In our exploratory brief report, we demonstrated that bisphosphonate intake was associated (approached statistically significant) with the reduced expansion of periarticular bone area over a 24-month follow-up, specifically in the medial tibia sub-regions.

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Author Contributions

All authors made substantial contributions to the design of the study, interpretation of data, and provided final approval for submission of the manuscript. Specifically, A.H.M, S.D., A.G., F.W.R., M.B., and P.G.C. made contributions to study conception and design. A.H.M. and S.D. performed the analyses, interpreted the results, and wrote the initial manuscript draft while all other authors revised it critically. All authors read and approved the final manuscript.

Role of the funding source

None

Conflict of interest

A.G. received money from MerckSerono, AstraZeneca, Genzyme, OrthoTrophix, and TissueGene for consulting; and received money from BICL as president and shareholder. F.W.R. received money from Boston Imaging Core Lab (BICL) as chief executive officer and shareholder. P.G.C. has consulted for Abbvie, Medivir, Merck Serono, Novartis, Samumed and TissueGene. . S.D. received money from Toshiba Medical Systems for consulting; S.D. received grants from GERRAF, and Carestream Health for a cone-beam computed tomographic clinical trial. None of the authors have any personal or financial relationships that could potentially influence the outcome of this work There is no conflict of interest for the rest of the authors.

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Table 1. Baseline characteristics of study population according to the history of bisphosphonates intake

	All FNIH female participants			PS-matched subjects		
	Bisphosphonate			Bisphosphonate		
	+ (n=56)	– (n=295)	*p-value*	+ (n=48)	– (n=105)	*p-value*
OA related factors						
Age						
45-55 years	3 (5.4 %)	96 (32.5 %)	**<0.001** *	3 (6.3%)	16 (15.2%)	0.943
55-65 years	22 (39.3 %)	109 (36.69 %)		19 (39.6%)	30 (28.6%)	
65-75 years	26 (46.4 %)	70 (23.7 %)		23 (47.9%)	44 (41.9%)	
>75 years	5 (8.9 %)	20 (6.8 %)		3 (6.3%)	15 (14.3%)	
BMI						
<25 kg/m^2	15 (26.8 %)	33 (11.3 %)	**<0.001** *	11 (22.9%)	17 (16.2%)	0.443
25-30 kg/m^2	19 (33.9 %)	85 (28.8 %)		18 (37.5%)	43 (41.0%)	
30-35 kg/m^2	18 (32.1 %)	104 (35.3 %)		15 (31.3%)	34 (32.4%)	
>35 kg/m^2	4 (7.1 %)	73 (24.7 %)		4 (8.3%)	11 (10.5%)	
WOMAC pain score (range: 0-16)						
0-1	25 (44.6 %)	168 (56.9 %)	0.538	21 (43.8 %)	61 (58.1 %)	0.244
2-10	30 (53.6 %)	113 (38.3 %)		26 (54.2 %)	39 (37.1 %)	
>10	1 (1.8 %)	14 (4.7 %)		1 (2.1 %)	5 (4.8 %)	
Radiographic KL grade (range: 0-4)						
1	10 (17.9 %)	36 (12.2 %)	0.604	8 (16.7 %)	13 (12.4 %)	0.939
2	29 (51.8 %)	172 (58.3 %)		26 (54.2 % %)	65 (61.9 %)	
3	17 (30.4 %)	87 (29.5 %)		14 (29.2 %)	27 (25.7 %)	
OP related factors						
Alcohol use (more than 3 times per week)	15 (26.8 %)	57 (19.5 %)	0.212	13 (27.1 %)	24 (22.9 %)	0.684
Smoking (positive history and current use)	1 (1.8 %)	20 (6.8 %)	0.220	1 (2.1 %)	3 (2.9 %)	1.00
History of bone fracture						
Any fracture after age 45	22 (39.3 %)	50 (17.1 %)	**<0.001** *	18 (37.5 %)	30 (28.6 %)	0.348
Hip fracture	0	2 (0.7 %)	1	0	0	1.00

Vertebrae/spine fracture	4 (7.3 %)	9 (3.1 %)	0.133	3 (6.3 %)	7 (6.7 %)	1.00
History of Oral Corticosteroids	2 (3.6 %)	2 (0.7 %)	0.121	1 (2.1 %)	2 (1.9 %)	1.00

Data were presented as Number (Percentage %). Data were compared using Chi-Square test with Fisher's exact test wherever applicable. FNIH: Foundation for the National Institute of Health PS: Propensity Score; OA: Osteoarthritis BMI: Body Mass Index; WOMAC: Western Ontario & McMaster Universities Osteoarthritis; KL: Radiographic Kellgren and Lawrence; OP: Osteoporosis.
False discovery rate adjustment p-value were calculated using Benjamini-Hochberg procedure. * adjusted p-value <0.001 (for all three marked p-values); all other adjusted p-values were >0.10.

Table 2. Association between the increasing change (expansion) of periarticular bone area and bisphosphonates intake

	OR (95%CI), *p-value*	
	per 1.96RCI	**per 1SDD**
Femur		
Medial	0.701 (0.379 – 1.295), 0.256	0.888 (0.436 – 1.811), 0.745
Lateral	0.795 (0.415 – 1.526), 0.491	0.576 (0.214 – 1.551), 0.275
Tibia		
Medial	**0.552 (0.309 – 0.986), 0.045 #**	**0.514 (0.271 – 0.975), 0.042 #**
Lateral	0.840 (0.488 – 1.448), 0.530	0.635 (0.336 – 1.267), 0.208
Patella		
Medial	0.725 (0.398 – 1.321), 0.293	0.737 (0.230 – 2.366), 0.608
Lateral	0.714 (0.392 – 1.303), 0.272	0.320 (0.093 – 1.104), 0.071
Trochlea		
Medial	0.925 (0.544 – 1.572), 0.773	0.739 (0.381 – 1.433), 0.370
Lateral	0.887 (0.458 – 1.716), 0.721	0.889 (0.421 – 1.874), 0.757
Notch	1.277 (0.706 – 2.308), 0.419	1.157 (0.597 – 2.245), 0.666

ORs were reported by comparing study groups (bisphosphonate + vs. bisphosphonate –) for the risk of increasing (expansion + vs. expansion –) in the periarticular bone area using conditional logistic regression analysis for each sub-region. The periarticular bone expansion was defined as an increase of more than 1SDD or 1.96RCI between 24-month and baseline values.
OR: Odds Ratio; CI: Confidence Interval; SDD: Standard Deviation of Difference; RCI: Reliable Change Index
False discovery rate adjusted p-value were calculated using Benjamini-Hochberg procedure. # adjusted p-value <0.10 (0.085 for both marked p-values, which is approached statistically significant); all other adjustment p-values were > 0.10.

Supplementary Table 1. MRI protocol acquisition parameters.

	Localizer	3D FLASH	2D MESE	3D DESS	2D TSE	2D TSE FS	Thigh axial
Weighting	-	T1W	Intermediate	T2	Intermediate	Intermediate	Intermediate
Fat Saturated	No	WE	No	WE	No	FS	No
Plane	3-plane	Coronal	Sagittal	Sagittal	Coronal	Sagittal	Axial
Matrix (phase)	128	512	269	307	307	313	512
Matrix (frequency)	256	512	384	384	384	448	512
Number of slices	21	80	21	160	35	37	15
FOV (mm)	200	160	120	140	140	160	500
Slice thickness (mm)	5/1	1.5/0	3/0.5	0.7	3	3	5
Flip angle (degree)	40	12	N/A	25	180	180	90
TE (ms)	5	7.57/20	10, 20, 30, 40, 50, 60, 70/2700	4.7	29	30	10
TR (ms)	10			13.6	3700	3200	500
Chemical shift (pixels)	1.8	0	1.8	0	1.3	0	2.2
Number of excitations averaged	1	1	1	1	1	1	1
Phase encode axis	A/P, R/L	R/L	A/P	A/P	R/L	A/P	A/P
Distance factor (%)	50	0	16	0	0	0	0
Phase oversampling	0	0	0	0	20	40	0
Slice oversampling	0	0	0	10	0	0	0
Phase resolution	50	100	70	80	80	70	50
Phase partial Fourier (8/8=1)	1	1	0.875	1	1	1	1
Readout partial Fourier (8/8=1)	1	1	1	1	1	1	1
Slice partial Fourier (8/8=1)	1	0.75	0.75	0.75	1	1	1
X-resolution (mm)	0.391	0.313	0.313	0.365	0.365	0.357	0.977
Y-resolution (mm)	0.781	0.313	0.446	0.456	0.456	0.511	0.977

Two-dimensional (2D); Three-dimensional (3D); Dual echo at steady state (DESS); Field of View (FOV); Fat Saturated (FS); Intermediate-weighted (IW); Echo time (TE); Repetition time (TR); Turbo spin-echo (TSE); Water-excitation (WE)

Supplementary Table 2. Baseline periarticular bone area (mm^2) and 3D shape (vector) in study population (females) according to the history of bisphosphonates intake

	Bisphosphonate + (n=48)	**Bisphosphonate – (n=105)**	**p-value**
Periarticular Bone Area (mm^2)			
Medial			
Femur	2188.6 ± 37.2	2154.9 ± 19.2	0.015
Tibia	1042.6 ± 15.5	1033.0 ± 8.8	0.270
Patella	519.8 (87.3)	499.3 (87.6)	0.396
Trochlea	626.2 ± 9.7	618.9 ± 5.4	0.100
Lateral			
Femur	1495.7 (247.69)	1493.0 (178.3)	0.677
Tibia	811.8 ± 12.2	802.6 ± 6.6	0.053#
Patella	658.4 (124.8)	635.1 (108.1)	0.347
Trochlear	1154.1 ± 16.5	1141.3 ± 10.1	0.461
Notch	1370.5 ± 22.6	1353.1 ± 12.98	0.124
Periarticular Bone 3D shape			
Femur	0.663 ± (1.38)	0.351 ± (1.64)	0.207
Tibia	-0.057 ± 0.18	-0.289 ± 0.11	0.462
Patella	0.247 ± 0.22	0.024 ± 0.16	0.948

Data were presented as Mean ± S.E.M. (standard error of the mean). (for normally distributed variables) or medians (Interquartile range, IQR) (for not normally distributed variables; marked by +). Data were compared using independent two sample t-test (when continuous variables were normally distributed), and Mann-Whitney test (when continuous variables were not normally distributed).

False discovery rate adjusted p-value were calculated using Benjamini-Hochberg procedure. # adjusted p-value <0.10 (0.085 for marked p-value, which is approached statistically significant); all other adjusted p-values were >0.10.

Supplementary Table 3. Interval changes (between 24-month and baseline) in periarticular bone area (mm2) in study population (females) according to the history of bisphosphonates intake

		Bisphosphonate + (n=48)	**Bisphosphonate – (n=105)**	**p-value**
Medial				
	Femur	-18.82 (38.3)	22.46(46.7)	0.134
	Tibia	-3.29 (22.3)	-14.97 (24.79)	**0.003***
	Patella	3.04 (12.8)	5.94 (12.6)	0.079
	Trochlea	6.65(11.5)	8.00 (13.3)	0.247
Lateral	Femur	8.83 (29.8)	11.51 (39.8)	0.408
	Tibia	7.61 (16.0)	9.23(17.7)	**0.019#**
	Patella	5.09 (20.5)	7.95(18.1)	**0.032**
	Trochlear	7.63(22.7)	9.57 (19.6)	0.112
	Notch	12.42 (28.9)	9.39 (26.9)	0.982

Data were presented as medians (Interquartile range, IQR) of changes in the periarticular bone area (mm2) for each anatomical sub-region (24-month minus baseline measurements). The analysis was performed using pairing Wilcoxon signed rank test.

False discovery rate adjusted p-value were calculated using Benjamini-Hochberg procedure. * adjusted p-value <0.05 (0.002 for marked p-value, which is statistically significant); # adjusted p-value <0.10, (0.076 for marked p-value, which is approached statistically significant): all other adjusted p-values were >0.10.

Supplementary Table 4. Interval changes (between 24-month and baseline) in periarticular bone 3D shape (vector) in study population according to the history of bisphosphonates intake

	Bisphosphonate + (n=48)	**Bisphosphonate – (n=105)**	**p-value**
Periarticular 3D shape			
Femur	-0.146 (025)	-0.177 (0.39)	**0.041**
Tibia	-0.245 (0.45)	-0.263 (0.50)	0.964
Patella	-0.081 (0.58)	-0.225 (0.80)	0.066

Data were presented as medians (Interquartile range, IQR) of changes in the periarticular bone are (mm2) for each anatomical sub-region (24-month minus baseline measurements). The analysis was performed using paired Wilcoxon signed rank test.

There is no false discovery rate adjusted p-value <0.10 (adjusted for multiple comparisons using Benjamini-Hochberg procedure).

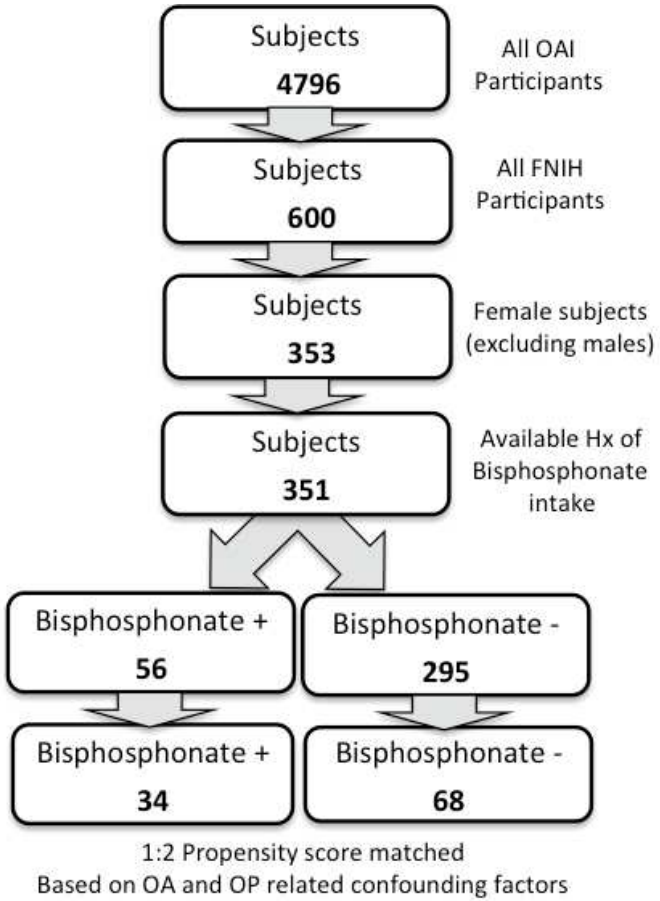
Supplementary Table 5. Association between the worsening of periarticular bone 3D shape and bisphosphonates intake

	OR (95% CI), p-value per 1.96 RCI	Per ISDD
Periarticular 3D shape		
Femur	-0.861(0.516-1.437), 0.568	-0.602 (0.296-1.222), 0.160
Tibia	1.094 (0.697-1.717), 0.697	-0.817 (0.406-1.642), 0.570
Patella	0.726 (0.421-1.253), 0.251	-0.563 (0.264-1.198), 0.136

ORs were reported by comparing study groups (bisphosphonate + vs. bisphosphonate -) for the risk of worsening in the periarticular bone 3D shape using conditional logistic regression analysis for each region. The periarticular bone 3D shape worsening was defined as an increase of more than ISDD or 1.96RCI between 24-month and baseline values.

OR: Odds Ratio: CI: Confidence Interval; SDD: Standard Deviation of Difference; RCI: Reliable Change Index

There is no false discovery rate adjusted p-value <0.10 (adjusted for multiple comparisons using Benjamini-Hochberg procedure).



Supplementary Figure 1. Flow diagram showing the selection of matched subjects for the study. OAI: Osteoarthritis Initiative; FNIH: Foundation for the National Institute of Health; Hx: History; OA: Osteoarthritis OP: Osteoporosis