BJR

■ CARTILAGE

Bisphosphonate use is associated with a decreased joint narrowing rate in the non-arthritic hip

T. Kawai,
K. Nishitani,
Y. Okuzu,
K. Goto,
Y. Kuroda,
S. Kuriyama,
S. Nakamura,
S. Matsuda

From Kyoto University Graduate School of Medicine, Kyoto, Japan

Aims

The preventive effects of bisphosphonates on articular cartilage in non-arthritic joints are unclear. This study aimed to investigate the effects of oral bisphosphonates on the rate of joint space narrowing in the non-arthritic hip.

Methods

We retrospectively reviewed standing whole-leg radiographs from patients who underwent knee arthroplasties from 2012 to 2020 at our institute. Patients with previous hip surgery, Kellgren–Lawrence grade ≥ II hip osteoarthritis, hip dysplasia, or rheumatoid arthritis were excluded. The rate of hip joint space narrowing was measured in 398 patients (796 hips), and the effects of the use of bisphosphonates were examined using the multivariate regression model and the propensity score matching (1:2) model.

Results

A total of 45 of 398 (11.3%) eligible patients were taking an oral bisphosphonate at the time of knee surgery, with a mean age of 75.8 years (SD 6.2) in bisphosphonate users and 75.7 years (SD 6.8) in non-users. The mean joint space narrowing rate was 0.04 mm/year (SD 0.11) in bisphosphonate users and 0.12 mm/year (SD 0.25) in non-users ($p < 0.001$). In the multivariate model, age (standardized coefficient = 0.0867, $p = 0.016$) and the use of a bisphosphonate (standardized coefficient = −0.182, $p < 0.001$) were associated with the joint space narrowing rate. After successfully matching 43 bisphosphonate users and 86 non-users, the joint narrowing rate was smaller in bisphosphonate users ($p < 0.001$).

Conclusion

The use of bisphosphonates is associated with decreased joint degeneration in non-arthritic hips after knee arthroplasty. Bisphosphonates slow joint degeneration, thus maintaining the thickness of joint cartilage in the normal joint or during the early phase of osteoarthritis.

Article focus

- Potential protective effects of bisphosphonates on cartilage in the hip joint.

Key messages

- Joint narrowing rate in the hip among patients undergoing total knee arthroplasty was smaller in patients taking bisphosphonates than in those who were not.
- Older age was weakly associated with increased joint narrowing, while BMI, sex, and side (knee arthroplasty side or contralateral side) were not.

Strengths and limitations

- This is the first study to evaluate the potential protective effects of bisphosphonates on hip joint degeneration in terms of joint space narrowing rate.
- This is a retrospective study with a small number of patients.

Introduction

Osteoarthritis (OA) is thought to be primarily a cartilage disease, but is currently recognized as a disease of the whole joint. Mechanical loading, several biomarkers in joint fluid, and growth factors may be

Correspondence should be sent to Toshiyuki Kawai; email: kawait@kuhp.kyoto-u.ac.jp

associated with progression of OA.[1-3] Additionally, periarticular bone abnormalities, such as decreased bone mineral content and increased bone metabolism derangement, are also related to its initiation and progression.[4] Subchondral bone is the bony component located distal to calcified cartilage.[5,6] Recent studies have suggested that changes in subchondral bone play an important role in the development and progression of OA.[6-8]

Bisphosphonates (BPs), introduced in 1996, are widely used for preventing and treating osteoporosis. BP use is associated with a significantly lower risk of total knee arthroplasty (TKA), suggesting that BPs are potentially beneficial in patients with knee OA.[9] When BPs make contact with osteoclasts, they impair the ability of the osteoclasts to form the ruffled border that facilitates adherence to the bony surface and produces the protons that are necessary for bone resorption.[10,11] Therefore, BPs decrease subchondral bone remodelling, possibly alleviating increased bone turnover in early OA.

Reviews on the effect of BPs in patients with OA suggest that they are effective in relieving pain and accelerating functional recovery.[12,13] There have only been a few studies that examined the effects of BPs on hip OA: a study in Taiwan showed that the use of BPs was not associated with a decreased risk of undergoing total hip arthroplasty (THA) in patients with hip OA.[14] There has only been one randomized controlled trial that evaluated the effect of BPs on hip OA, which was conducted in patients who had hip OA with an average age of 54 years. It showed that alendronate decreased pain at one and two years of follow-up, but failed to prevent progression of hip OA in a radiological evaluation.[13] However, these two studies were performed in patients who had established hip OA. Because previous studies have shown that narrowing in the hips depends on the severity of arthritic change, detecting the effects of a drug on OA progression in patients with hip OA of various severities would be difficult. As increased joint space narrowing rates were associated with progression of hip OA,[15,16] interventions that can reduce the joint space narrowing rate would have clinical importance. To the best of our knowledge, no studies have examined the effects of BPs on non-arthritic hips.

Therefore, this study aimed to investigate whether BPs have protective effects on articular cartilage in non-arthritic hips, by measuring the rate of hip joint space narrowing. We hypothesize that BPs will help to maintain the volume of joint cartilage in non-arthritic hips via decreased remodelling of subchondral bone.

Methods

This retrospective study was conducted by reviewing the medical records and whole-leg standing radiographs of patients who underwent a knee arthroplasty at our institute. All patients provided informed consent, and the study protocol was approved by the institutional review board of our hospital. Patients undergoing knee arthroplasty were selected for analysis in this study because they appeared to be suitable for evaluation of the effects of patients' factors on hip joint degeneration. These patients were included because they routinely had whole-leg standing radiographs performed before and after surgery, and the majority of them did not have a hip aetiology.

From February 2012 to March 2020, 670 patients underwent primary TKA or unicondylar knee arthroplasty. All patients were asked about their medications several weeks before hospitalization.

Of the 670 patients, 66 were excluded because they lacked available radiographs that included measurable hip joints at more than one year after knee arthroplasty; they had a history of hip surgery, rheumatoid arthritis, hip OA (Kellgren–Lawrence grade ≥ II),[17] hip dysplasia (centre-edge angle < 15°), or use of teriparatide or denosumab; they were taking corticosteroids; or they lacked available postoperative whole-leg standing radiographs. The final cohort comprised 398 (796 hips) patients in whom the joint space width of both hips was measurable preoperatively and at > one year postoperatively (Figure 1). These patients were divided into the BP group and the control group. Patients were categorized as the BP group if they were using a BP at the time of hospitalization. If patients were not taking BP medication at the time of hospitalization, they were allocated to the control group. Overall, 45 patients were taking BPs, among whom alendronate 35 mg/week was used in 20, risedronate 17.5 mg/week was used in 14, risedronate 2.5 mg/day was used in three, and minodronate 50 mg/month was used in eight.

Among the 398 patients, 255 underwent knee arthroplasty on one side, while the remaining 143 had surgery on both sides during the study. In those who underwent surgeries on both sides, measurements were conducted using radiographs before the first surgery and at the final follow-up. Anteroposterior standing radiographs of the whole legs (including the pelvis) were standardized for the beam position and radiological penetration, and were routinely obtained preoperatively and postoperatively.

Measurement of the joint narrowing rate. Joint narrowing was measured on standing radiographs as described by Kawai et al.[18] Briefly, the joint space width was defined as the narrowest point between the cortical surface of the acetabulum and the bone contour of the femoral head on a digitized image using web-based Centricity software (GE Healthcare, USA). The hip joint was magnified to fit the display (Figure 2). The joint space narrowing rate (JSNR) was defined as the decrease in joint space width between the preoperative visit and the latest follow-up radiographs divided by the time (in years) between the two radiographs.

To calibrate the magnification of the radiograph and normalize the effects of body size, the decrease in the ratio of the joint space width to the size of the femoral
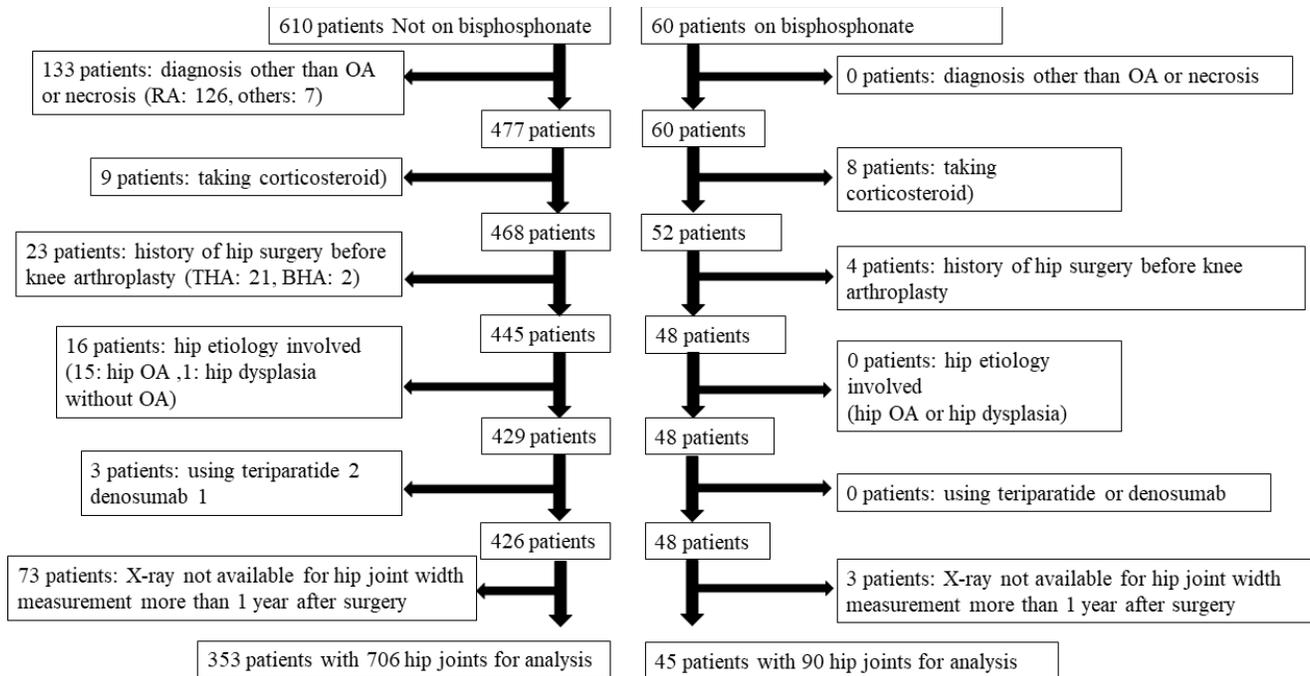
```
┌─────────────────────────────────┐          ┌───────────────────────────────┐
│ 610 patients Not on bisphosphonate │        │ 60 patients on bisphosphonate │
└─────────────────────────────────┘          └───────────────────────────────┘
```

┌──────────────────────────────────────┐   ┌──┐
│ 133 patients: diagnosis other than OA │   │ 0 patients: diagnosis other than OA or necrosis │
│ or necrosis (RA: 126, others: 7)   │   └──┘
└──────────────────────────────────────┘

477 patients   60 patients

┌──────────────────────────────────────┐   ┌──────────────────────────────┐
│ 9 patients: taking corticosteroid)   │   │ 8 patients: taking corticosteroid) │
└──────────────────────────────────────┘   └──────────────────────────────┘

468 patients   52 patients

┌──┐   ┌──┐
│ 23 patients: history of hip surgery before │   │ 4 patients: history of hip surgery before knee │
│ knee arthroplasty (THA: 21, BHA: 2)   │   │ arthroplasty   │
└──┘   └──┘

445 patients   48 patients

┌──┐   ┌──┐
│ 16 patients: hip etiology involved   │   │ 0 patients: hip etiology involved   │
│ (15: hip OA ,1: hip dysplasia without OA) │   │ (hip OA or hip dysplasia)   │
└──┘   └──┘

429 patients   48 patients

┌──┐   ┌──┐
│ 3 patients: using teriparatide 2   │   │ 0 patients: using teriparatide or denosumab │
│ denosumab 1   │   └──┘
└──┘

426 patients   48 patients

┌──┐   ┌──┐
│ 73 patients: X-ray not available for hip joint width │   │ 3 patients: X-ray not available for hip joint width │
│ measurement more than 1 year after surgery │   │ measurement more than 1 year after surgery │
└──┘   └──┘

┌──┐   ┌──┐
│ 353 patients with 706 hip joints for analysis │   │ 45 patients with 90 hip joints for analysis │
└──┘   └──┘

Fig. 1

Flow chart showing inclusion and exclusion of patients. BHA, bipolar hip arthroplasty; RA, rheumatoid arthritis; OA, osteoarthritis; THA, total hip arthroplasty.

head was also calculated as described by Kawai et al.[19] The change in the ratio was divided by the follow-up period to calculate the normalized JSNR (nJSNR) as shown below.

$$nJSNR = \frac{\left(\frac{JSW1}{D1} - \frac{JSW2}{D2}\right)}{follow-up\ duration\ in\ years} \times 1000,$$

where JSW1 and JSW2 are the joint space widths before knee arthroplasty and at the final follow-up, respectively, and D1 and D2 are the diameters of the femoral head measured on radiographs obtained one month before knee arthroplasty and at the final follow-up, respectively (Figures 2c and 2d).

Interpretations were performed in random order by an experienced orthopaedic surgeon (TK) blinded to the use of BPs. The inter- and intrareader reliabilities were assessed in a random sample of 40 joints. For evaluating the inter-reader reliability, the images were reviewed by another experienced hip surgeon (YO) who was blinded to the patients' information.

Statistical analysis. Differences in proportions were calculated using the Pearson chi-squared test. Differences in means were calculated using the Mann-Whitney U test for the comparison of two groups or the Kruskal-Wallis test for comparisons of > two groups. Univariate and multivariate regression analyses were performed to determine the independent association of the rate of hip joint space narrowing with each of the following factors: sex, age, BMI, indication (presence of knee OA), use of vitamin D, type of arthroplasty (TKA or unicondylar), and use of BPs. Interactions were quantified using variance inflation factors, with values of five to ten indicating collinearity. Significance was set at $p < 0.05$. Logistic regression was used to compute the propensity of taking a BP at the time of the surgery. Patients' demographic factors (age, sex, BMI, follow-up duration, diagnosis of knee OA, use of vitamin D, and type of arthroplasty (TKA or not TKA)) were used as covariates in the propensity score. Patients taking a BP were matched to those not taking a BP using calipers of a width equal to 0.2 of the standard deviation (SD) of the logit of the propensity score. A 1:2 ratio was used for matching. Standardized mean differences (SMDs) for all covariates were estimated before and after matching, and balance was considered to be achieved when the SMD was < 0.1.[20] Whether matching was successful was judged on the basis of the proportion of patients matched and the balance of covariates after matching. Additional analysis was performed to compare the joint narrowing rate in hip joints between ipsilateral and contralateral to the knee arthroplasty. This analysis was conducted in 255 patients who underwent knee arthroplasty only on one side during the study period. All statistical analyses were performed using JMP Pro 15 software (SAS Institute, USA).

Results

The intraclass correlation coefficients (ICCs) for inter- and intrareader reliability of the femoral head size were 0.97 and 0.99, respectively. The ICCs for inter- and intrareader reliabilities of the joint space measurements were 0.88 and 0.92, respectively. The patients' demographic data are shown in Table I. The mean JSNR was significantly higher in the control group (0.125 mm/year (SD 0.205)) than in the BP group (0.041 mm/year (SD 0.110), p <
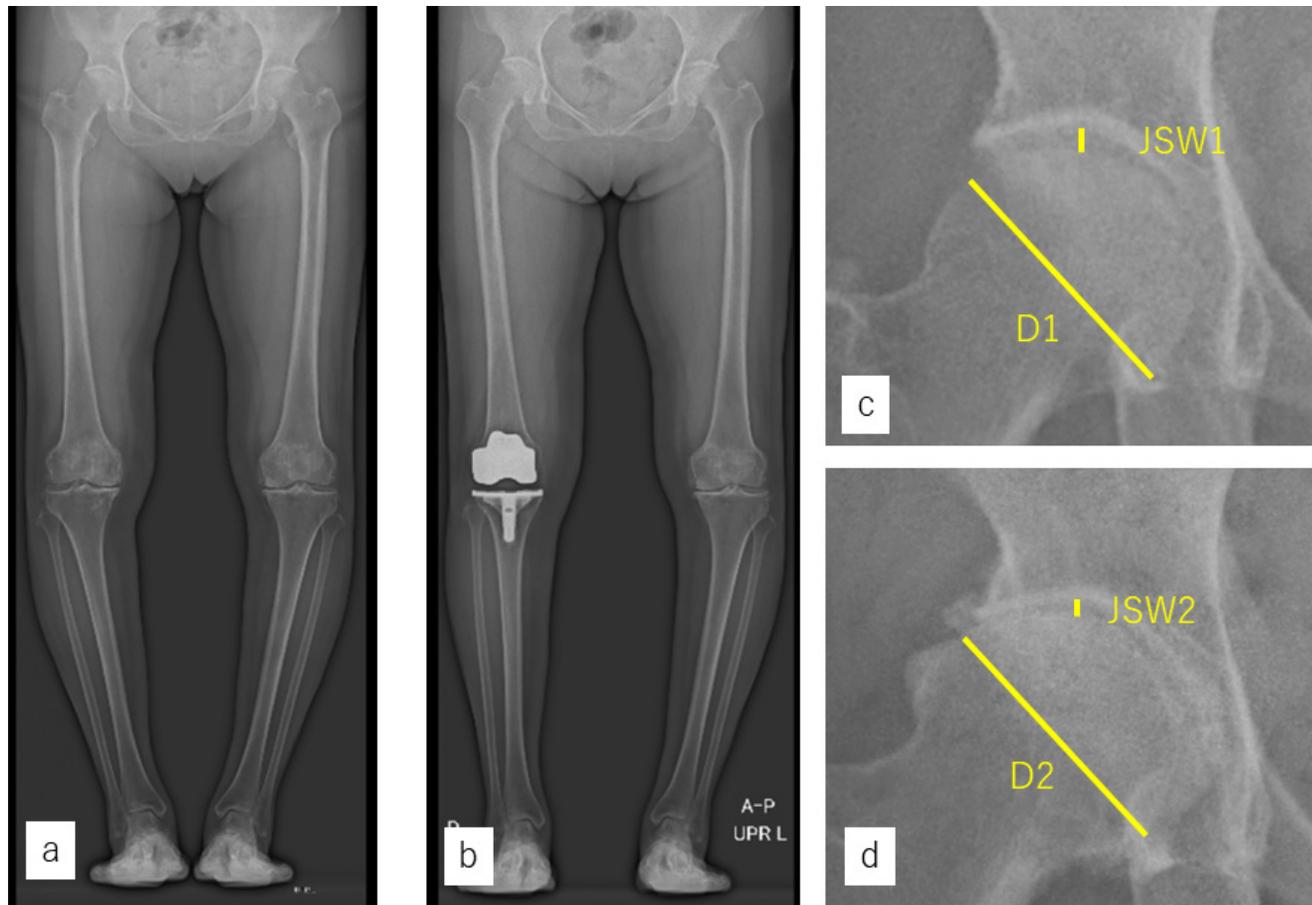
Fig. 2

Measurements of the hip joint space width in a representative case. A 65-year-old woman underwent total knee arthroplasty for osteoarthritis (OA) (bisphosphonate non-user). a) Anteroposterior standing whole-leg radiograph taken before surgery. b) Anteroposterior standing whole-leg radiograph taken at four years after surgery. c) Magnified image of the area including the right hip in panel a). d) Magnified image of the area including the right hip in panel b). The joint space width and the femoral head diameter were measured as indicated by the yellow lines. JSW1 and JSW2 are the joint space widths before surgery and at the final follow-up, respectively. D1 and D2 are the femoral head diameters measured on radiographs at three months after surgery and at the final follow-up, respectively.

0.001, Mann-Whitney U test) (Figure 3a). The mean nJSNR was significantly higher in the control group (2.699 mm/year (SD 4.031)) than in the BP group (0.366 mm/year (SD 2.754), p < 0.001, Mann-Whitney U test) (Figure 3d).

Univariate regression analyses performed using data from all patients showed that the nJSNR was associated with age and the use of BPs (Table II). Multivariate regression analysis also showed that a younger age (p = 0.016, least squares method) and the use of BPs (p < 0.001, least squares method) were associated with a smaller nJSNR (Table II). There was no significant difference in the JSNR or nJSNR between the ipsilateral and contralateral hips (Figure 4).

Table III shows the patients' data and JSNRs for each type of BP. Although patients who used alendronate had a significantly higher BMI than those who used two BPs, there were no differences in sex, age, follow-up period, diagnosis, use of vitamin D, or type of arthroplasty among the three groups. There was no significant difference in the JSNR or nJSNR among the three types of BPs.

After successfully matching 43 BP users and 86 non-BP users, the JSNR and nJSNR were significantly lower in the BP group than in the control group (both p < 0.001, Mann-Whitney U test) (Table IV).

Discussion

In this retrospective study performed in patients who had non-arthritic hips, the use of BPs was associated with a lower JSNR in the hip.

Patients undergoing knee arthroplasty were selected for this study because they regularly had whole-leg radiographs performed, which enabled longitudinal evaluation of non-arthritic hips. The mean JSNR in all patients was 0.114 mm/year (SD 0.182) for joints categorized as Kellgren–Lawrence grade 0 or 1, with the feature of no definite narrowing or osteophytes. Other researchers who measured joint space narrowing in the hips of patients with OA obtained mean rates of 0.13 to 0.30 mm/year.[21–24] Among patients who underwent THA for hip OA, the preoperative JSNR was 0.43 mm/

Table I. Demographic details and joint narrowing rates of all 398 patients before matching.

Variable	All subjects (398 patients, 796 hips)	Control (353 patients, 706 hips)	Bisphosphonate (45 patients, 90 hips)	p-value	SMD
Female sex, n (%)	309 (77.6)	267 (75.6)	42 (93.3)	0.00729*	0.504
Mean age, yrs (SD, range)	75.7 (6.8, 52 to 91)	75.7 (6.9, 52 to 91)	75.8 (6.2, 65 to 87)	0.850†	0.023
Mean BMI, kg/m^2 (SD, range)	26.0 (4.10, 13.8 to 42.8)	26.2 (4.0, 16.5 to 42.8)	24.6 (4.4, 13.8 to 36.6)	< 0.001†	0.398
Mean follow-up, yrs (SD, range)	3.05 (1.76, 1.00 to 10.28)	3.03 (1.72, 1.00 to 10.28)	3.30 (1.94, 1.00 to 9.18)	0.485†	0.086
Diagnosis KOA, n (%)	390 (98.0)	346 (98.0)	44 (97.8)	0.914*	0.014
Vitamin D, n (%)	43 (10.8)	32 (9.1)	11 (24.4)	0.00175*	0.419
TKA, n (%)	348 (87.4)	308 (87.3)	40 (88.8)	0.755*	0.049
Mean JSNR, mm/yr (SD, range)	0.114 (0.182, -0.248 to 2.841)	0.125 (0.205, -0.248 to 2.841)	0.041 (0.110, -0.154 to 0.623)	< 0.001†	
Mean nJSNR, mm/yr (SD, range)	2.435 (3.975, -12.775 to 57.830)	2.699 (4.031, -5.865 to 57.830)	0.366 (2.754, -12.775 to 7.723)	< 0.001†	

*Pearson chi-squared test.

†Mann-Whitney U test.

JSNR, joint space narrowing rate; KOA, knee osteoarthritis; nJSNR, normalized joint space narrowing rate; SD, standard deviation; SMD, standardized mean difference; TKA, total knee arthroplasty.

year (SD 0.43).[16] The JSNR in this study was slightly lower than that reported in previous studies. The main reason for this difference between studies could be that we excluded patients with hip OA and those with dysplasia of the hip and contralateral hip after unilateral THA, which could have resulted in a higher JSNR. A Kellgren–Lawrence radiological grade ≥ II is associated with a more rapid decline in the joint space width of the hip.[15]

In this study, BMI was not associated with the JSNR, which is consistent with a previous study by Kawai et al.[18] However, making a conclusion about the effect of BMI is difficult because the mean BMI of 26.0 kg/m^2 in this study was relatively low.

Previous studies showed that women had a narrower joint space width than men.[25,26] Only a few reports have shown the effects of sex on the JSNR. One study performed on patients who underwent spinal fusion showed that women had a higher JSNR, which was normalized by the size of the femoral head, than men.[18] In another study, sex was not associated with the JSNR,[15] although this measure was not adjusted for the size of the body or femoral head. In the present study, there was no significant difference in JSNR normalized by the size of the femoral head between men and women. Although the slight difference among the previous studies and the present study may be due to differences in the background characteristics between patients undergoing spinal fusion and knee arthroplasty, it would be difficult to draw a conclusion regarding the effects of sex on JSNR in the present study.

An older age was associated with increased joint space narrowing in the present study. However, the joint space width itself was not associated with age in two previous studies.[25,27] The mean age of patients in these studies ranged from 44 to 51 years, while the mean age in the present study was 75.7 years (SD 6.8).

The difference in the mean age between the present study and these previous reports might have led to the difference in results.

The use of vitamin D was not associated with the JSNR in our study. Previous studies have shown that vitamin D has the potential to improve symptoms of knee OA, but it only has a few structural effects.[28–31]

The BP group had a significantly lower JSNR than the control group in this study. This finding was confirmed in the multivariate model for all cohorts and in the comparison between BP users and propensity score-matched non-users. This is the first study to examine the effects of BPs on joint narrowing in non-arthritic hips. Previous reports that examined the effect of BPs mainly focused on their effects on knee OA. A study in Taiwan showed that BP users had a lower risk of knee arthroplasty than non-users of BPs, which suggested a potential beneficial effect of BPs on knee OA.[9,32]

A meta-analysis suggested that alendronate reduced hip pain,[31] while another systematic review concluded that the evidence of a reduction in pain was still limited.[33] Several trials on BPs focused primarily on medium-term and short-term structural endpoints, such as the joint space width on radiographs and bone marrow lesions on MRI, and the majority did not show a protective effect.[12,34,35] A trial of risedronate for knee OA with a one-year follow-up suggested symptom benefits, and minimal non-significant structure benefits based on the joint space width on radiographs.[12]

There have only been a few studies on the effects of BPs on hip OA. A study that used an insurance database in Taiwan showed that the use of BPs had a relatively lower risk of THA in patients with hip OA, but the effect was not significant (hazard ratio 0.783, 95% confidence interval 0.576 to 1.065; p = 0.11).[14] There has only been one randomized clinical trial that evaluated the effect of BPs on hip OA. This trial included patients with an
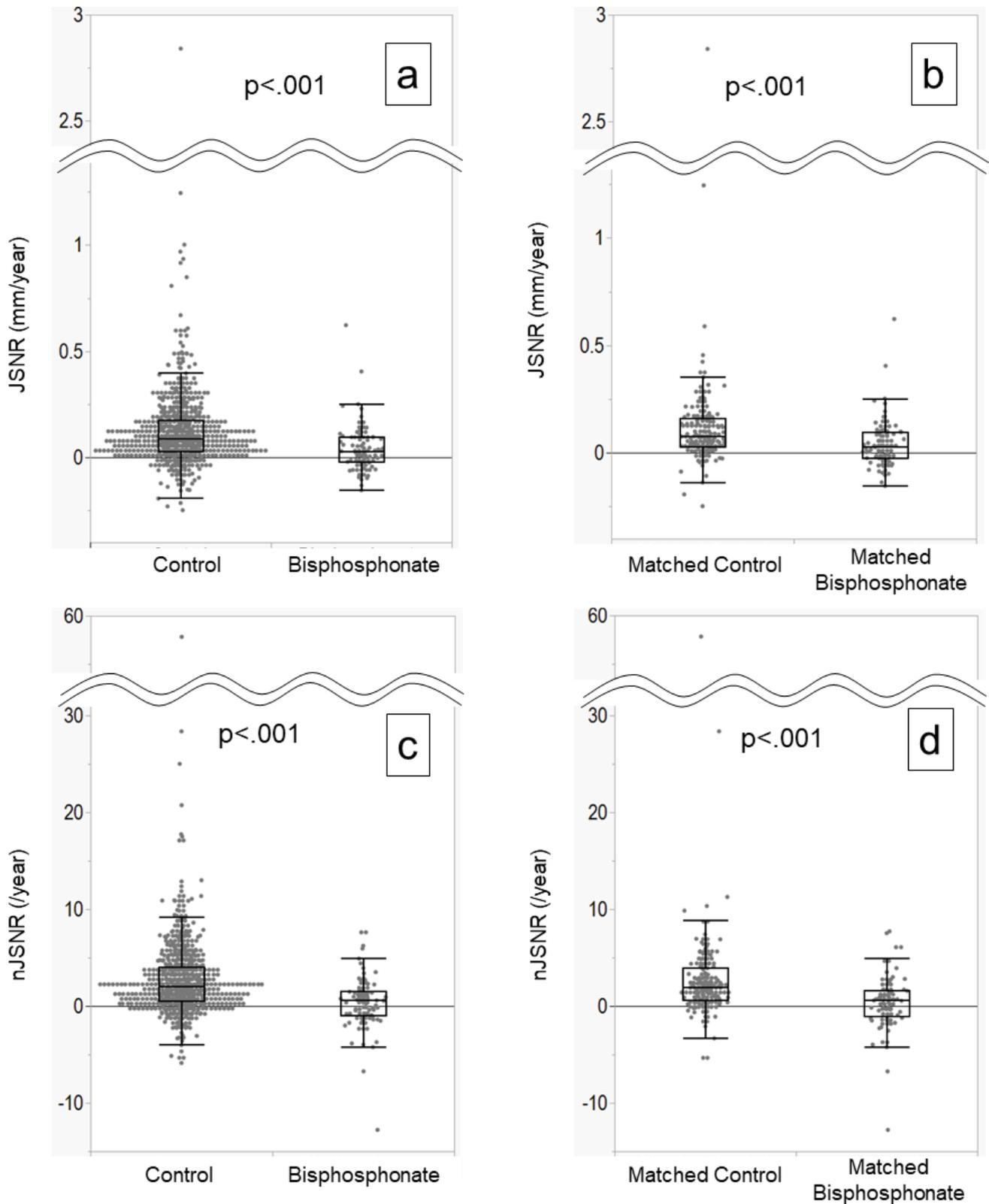
Fig. 3

Box and whisker plots of the control and bisphosphonate groups. a) Comparison of the joint space narrowing rate (JSNR) before matching between the groups. b) Comparison of the JSNR after matching between the groups. c) Comparison of the normalized JSNR (nJSNR) before matching between the groups. d) Comparison of the nJSNR after matching between the groups. The top and bottom of the boxes indicate the interquartile range, the line within the box indicates the median, and the whiskers represent points within 1.5 times the width of the interquartile range. All p-values were calculated using Mann-Whitney U test.

Table II. Univariate and multivariate regression performed for all patients.

Variable	Univariate				Multivariate				
	t	Standard error	Standardized coefficients β	p-value	t	Standard error	Standardized coefficients β	p-value	VIF
Sex (female)	-1.86	0.3395	-0.0659	0.0636	-1.20	0.3404	-0.0427	0.231	1.039
Age	2.42	0.0206	0.0854	0.0160	2.41	0.0209	0.0867	0.0164	1.062
BMI (kg/m^2)	-0.16	0.0346	-0.00569	0.873	-0.29	0.0352	-0.0104	0.774	1.073
Diagnosis KOA	-0.99	1.0039	-0.0350	0.325	-1.15	1.0113	-0.0411	0.252	1.052
Vitamin D	-1.05	0.4538	-0.0374	0.292	-0.29	0.456	-0.0104	0.774	1.058
Type of arthroplasty (TKA)	0.74	0.4252	0.0262	0.460	1.15	0.429	0.0412	0.251	1.053
Bisphosphonate	-5.33	0.4374	-0.186	< 0.001	-5.07	0.450	-0.182	< 0.001	1.060

JSNR, joint space narrowing rate; KOA, knee osteoarthritis; nJSNR, normalized joint space narrowing rate; TKA, total knee arthroplasty; VIF, variance inflation factor.
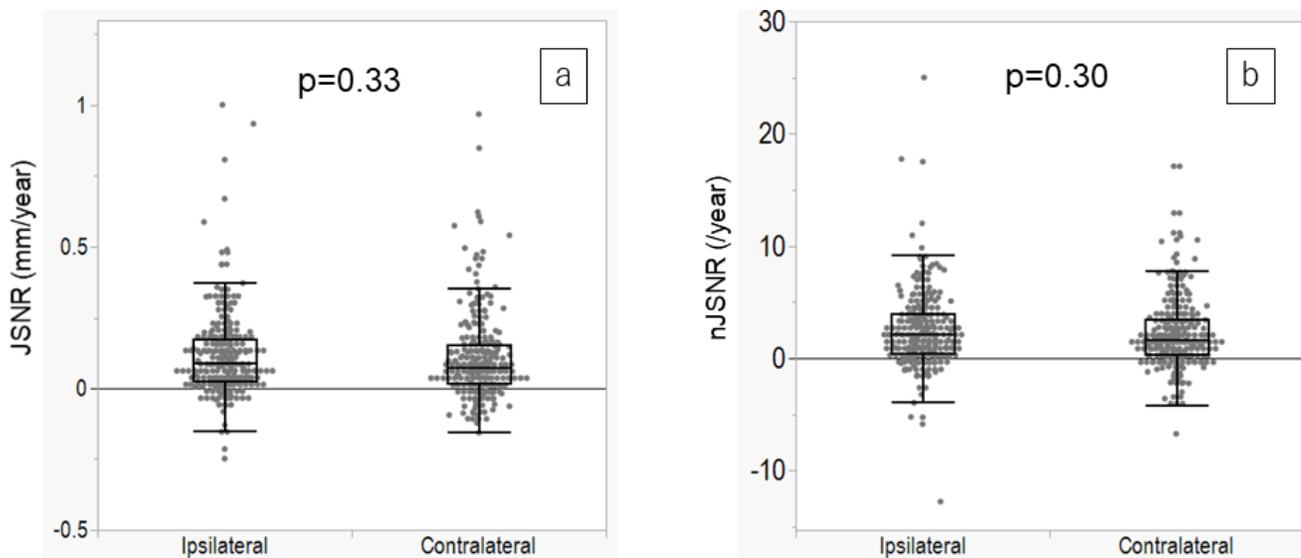
Fig. 4

Box and whisker plots showing comparison of a) the joint space narrowing rate (JSNR) and b) the normalized JSNR (nJSNR) between ipsilateral and contralateral hips to the side of knee arthroplasty. Analyses were performed in 255 patients who underwent knee arthroplasty on only one side during the study period. Both p-values were calculated using Mann-Whitney U test.

average age of 54 years, and showed that alendronate decreased pain at one and two years of follow-up, but failed to prevent progression of hip OA in a radiological evaluation.[13] However, this trial involved young patients and a small number (n = 42) of patients in the entire cohort. In the present study, we included older patients (mean age 75.7 years (SD 6.8)) who had non-arthritic hips, and patients with hip OA or dysplasia were excluded.

The largest difference between the previous studies mentioned above and the current study is the arthritic condition of the patients. The JSNR for established hip OA tends to be higher than that in non-arthritis hips.[16] In the present study, hips with Kellgren–Lawrence grade ≥ II were excluded. This might explain the difference in results in this study and two previous studies, which showed that preventive effects of BPs were limited.[13,14]

In early-stage OA, the subchondral plate beneath the articular cartilage becomes thinner as a result of increased bone remodelling.[6] These changes can be important components of the pathogenetic process that leads to OA. If a drug can slow bone remodelling in subchondral bone, it potentially delays or suppresses the initiation of OA in the non-arthritic joint. The decreased joint narrowing in non-arthritic hips in BP users in this study could have been due to the anti-porotic effects of BPs.

Although previous studies involving intra-articular injections of parathyroid hormone in a pig OA model and intra-articular injection of mesenchymal stem cells in patients with knee OA provided encouraging results,[36,37] it would be more widely accepted if administration of oral BPs alone could slow disease progression in the early phase of OA.

Table III. Patient demographic details and joint narrowing rates for each type of bisphosphonate.

Variable	Alendronate (20 patients, 40 hips)	Minodronate (8 patients, 16 hips)	Risedronate (17 patients, 34 hips)	p-value
Female sex, n (%)	17 (85.0)	8 (100)	17 (100)	0.134*
Mean age, yrs (SD, range)	76.2 (7.0, 65 to 87)	74.6 (6.3, 67 to 85)	76.0 (5.1, 65 to 86)	0.724‡
Mean BMI, kg/m^2 (SD, range)	26.5 (4.3, 19.2 to 36.6)	23.5 (2.6, 20.3 to 28.0)	24.6 (4.4, 13.8 to 30.6)	0.031†‡
Mean follow-up, yrs (SD, range)	3.17 (2.06, 1.00 to 9.18)	2.96 (1.18, 1.73 to 5.17)	3.62 (2.05, 1.00 to 7.99)	0.583‡
Diagnosis KOA, n (%)	19 (95)	8 (100)	17 (100)	0.528*
Vitamin D, n (%)	16 (80.0)	5 (62.5)	13 (76.5)	0.619*
TKA, n (%)	18 (90.0)	7 (87.5)	15 (88.2)	0.976*
Mean JSNR, mm/yr (SD, range)	0.018 (0.076, -0.154 to 0.141)	0.053 (0.078, -0.249 to 0.251)	0.063 (0.147, -0.104 to 0.623)	0.470‡
Mean nJSNR, mm/yr (SD, range)	0.214 (2.277, -4.235 to 7.534)	1.341 (1.794, -0.867 to 6.232)	0.087 (3.507, -12.775 to 7.723)	0.174‡

*Pearson chi-squared test.
†p < 0.05 for alendronate vs minodronate and for alendronate vs risedronate.
‡Kruskal-Wallis test.
JSNR, joint space narrowing rate; KOA, knee osteoarthritis; nJSNR, normalized joint space narrowing rate; SD, standard deviation; SMD, standardized mean difference; TKA, total knee arthroplasty.

Table IV. Demographic data and joint narrowing rates after 1:2 matching.

Variable	Control (86 patients, 172 hips)	Bisphosphonate (43 patients, 86 hips)	p-value	SMD
Female sex, n (%)	79 (91.9)	40 (93.0)	0.816	0.0042
Mean age, yrs (SD, range)	76.2 (6.6, 52 to 91)	76.1 (6.1, 65 to 87)	0.810†	0.009
Mean BMI, kg/m^2 (SD, range)	24.7 (3.7, 16.5 to 35.6)	24.9 (4.2, 13.8 to 36.6)	0.784†	0.041
Mean follow-up duration, yrs (SD, range)	3.37 (1.88, 1.00 to 10.27)	3.35 (1.98, 1.00 to 9.18)	0.964†	0.010
Diagnosis KOA, n (%)	83 (96.5)	42 (97.7)	0.720	0.072
Vitamin D, n (%)	20 (23.3)	10 (23.3)	1.000	0
TKA, n (%)	74 (86.0)	38 (88.4)	0.713	0.072
Mean JSNR, mm/yr (SD, range)	0.12 (0.25, -0.25 to 2.84)	0.04 (0.11, -0.15 to 0.62)	< 0.001†	
Mean nJSNR, mm/yr (SD, range)	2.682 (5.331, -5.449 to 57.830)	0.349 (2.810, -12.775 to 7.723)	< 0.001†	

*Pearson chi-squared test.
†Mann-Whitney U test.
JSNR, joint space narrowing rate; KOA, knee osteoarthritis; nJSNR, normalized joint space narrowing rate; SD, standard deviation; SMD, standardized mean difference; TKA, total knee arthroplasty.

There are several limitations to this study. First, this study had a small sample size and retrospective design. Second, the patients underwent knee arthroplasty. Although they had radiologically non-arthritic hips, they may not represent healthy subjects. A prospective, observational study of healthy subjects with non-arthritic hips is required to confirm the relationship between BPs and joint degeneration. In addition, some patients may have received correction of their knee alignment during the arthroplasty, which may have altered the direction of the mechanical force applied on the femoral head. However, the effects of alterations in knee alignment could be limited in this cohort because there was no difference in JSNR between the knee arthroplasty side and the contralateral side. Third, this study did not include measurements of bone mineral density or the thickness of the subchondral plate. These parameters should be considered in future prospective studies. Fourth, the compliance and duration of BP use were not analyzed. Although the half-life of BPs is longer than ten years, and the effects do not disappear soon after discontinuation,[38] the length of time patients continued to take these drugs was not recorded. Finally, the lack of evaluation of pain or function scores for the hip is also a limitation.

In summary, this retrospective study shows that the use of BPs is associated with a decreased JSNR in non-arthritic hips. BPs may have protective effects on joint cartilage in the normal joint or during the early phase of OA.

References

1. **He Z**, **Nie P**, **Lu J**, **et al**. Less mechanical loading attenuates osteoarthritis by reducing cartilage degeneration, subchondral bone remodelling, secondary inflammation, and activation of NLRP3 inflammasome. *Bone Joint Res*. 2020;9(10):731–741.
2. **Akhbari P**, **Karamchandani U**, **Jaggard MKJ**, **et al**. Can joint fluid metabolic profiling (or "metabonomics") reveal biomarkers for osteoarthritis and inflammatory joint disease?: A systematic review. *Bone Joint Res*. 2020;9(3):108–119.
3. **Duan M**, **Wang Q**, **Liu Y**, **Xie J**. The role of TGF-β2 in cartilage development and diseases. *Bone Joint Res*. 2021;10(8):474–487.
4. **Xing RL**, **Zhao LR**, **Wang PM**. Bisphosphonates therapy for osteoarthritis: a meta-analysis of randomized controlled trials. *Springerplus*. 2016;5(1):1704.

5. **Madry H**, **van Dijk CN**, **Mueller-Gerbl M**. The basic science of the subchondral bone. *Knee Surg Sports Traumatol Arthrosc*. 2010;18(4):419–433.

6. **Burr DB**, **Gallant MA**. Bone remodelling in osteoarthritis. *Nat Rev Rheumatol*. 2012;8(11):665–673.

7. **Goldring MB**, **Goldring SR**. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann N Y Acad Sci*. 2010;1192:230–237.

8. **Weber A**, **Chan PMB**, **Wen C**. Do immune cells lead the way in subchondral bone disturbance in osteoarthritis? *Prog Biophys Mol Biol*. 2019;148:21–31.

9. **Neogi T**, **Li S**, **Peloquin C**, **Misra D**, **Zhang Y**. Effect of bisphosphonates on knee replacement surgery. *Ann Rheum Dis*. 2018;77(1):92–97.

10. **Sato M**, **Grasser W**, **Endo N**, **et al**. Bisphosphonate action. Alendronate localization in rat bone and effects on osteoclast ultrastructure. *J Clin Invest*. 1991;88(6):2095–2105.

11. **Colucci S**, **Minielli V**, **Zambonin G**, **et al**. Alendronate reduces adhesion of human osteoclast-like cells to bone and bone protein-coated surfaces. *Calcif Tissue Int*. 1998;63(3):230–235.

12. **Spector TD**, **Conaghan PG**, **Buckland-Wright JC**, **et al**. Effect of risedronate on joint structure and symptoms of knee osteoarthritis: results of the BRISK randomized, controlled trial [ISRCTN01928173]. ISRCTN01928173. *Arthritis Res Ther*. 2005;7(3):R625–33.

13. **Nishii T**, **Tamura S**, **Shiomi T**, **Yoshikawa H**, **Sugano N**. Alendronate treatment for hip osteoarthritis: prospective randomized 2-year trial. *Clin Rheumatol*. 2013;32(12):1759–1766.

14. **Hung C-C**, **Wang C-Y**, **Fu S-H**, **Yang R-S**, **Hsiao F-Y**. Effects of anti-osteoporosis medications on total hip arthroplasty risks in osteoporotic patients with hip osteoarthritis in Taiwan: a nationwide cohort study. *Arch Osteopros*. 2018;13(1):107.

15. **Goker B**, **Doughan AM**, **Schnitzer TJ**, **Block JA**. Quantification of progressive joint space narrowing in osteoarthritis of the hip: longitudinal analysis of the contralateral hip after total hip arthroplasty. *Arthritis Rheum*. 2000;43(5):988–994.

16. **Conrozier T**, **Jousseaume CA**, **Mathieu P**, **et al**. Quantitative measurement of joint space narrowing progression in hip osteoarthritis: a longitudinal retrospective study of patients treated by total hip arthroplasty. *Br J Rheumatol*. 1998;37(9):961–968.

17. **KELLGREN JH**, **LAWRENCE JS**. Radiological assessment of osteo-arthrosis. *Ann Rheum Dis*. 1957;16(4):494–502.

18. **Kawai T**, **Shimizu T**, **Goto K**, **et al**. Number of levels of spinal fusion associated with the rate of joint-space narrowing in the hip. *J Bone Joint Surg Am*. 2021;103-A(11):953–960.

19. **Kawai T**, **Shimizu T**, **Goto K**, **et al**. The impact of spinopelvic parameters on hip degeneration after spinal fusion. *Spine (Phila Pa 1976)*. 2022;47(15):1093–1102.

20. **Austin PC**. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083–3107.

21. **Vignon E**. Results of the ECHODIAH clinical trial on hip arthrosis. *Presse Med*. 2002;31(1 Pt 2):7–9.

22. **Lequesne M**. Rapidly progressing destructive diseases of the hip. *Ann Radiol (Paris)*. 1993;36(1):62–64.

23. **Dougados M**, **Nguyen M**, **Berdah L**, **et al**. Evaluation of the structure-modifying effects of diacerein in hip osteoarthritis: ECHODIAH, a three-year, placebo-controlled trial. *Arthritis Rheum*. 2001;44(11):2539–2547.

24. **Conrozier T**, **Tron AM**, **Vignon E**. Coxarthroses. *Rev Prat*. 1996;46(18):2201–2205.

25. **Goker B**, **Sancak A**, **Arac M**, **Shott S**, **Block JA**. The radiographic joint space width in clinically normal hips: effects of age, gender and physical parameters. *Osteoarthritis Cartilage*. 2003;11(5):328–334.

26. **Lanyon P**, **Muir K**, **Doherty S**, **Doherty M**. Age and sex differences in hip joint space among asymptomatic subjects without structural change: implications for epidemiologic studies. *Arthritis Rheum*. 2003;48(4):1041–1046.

27. **Lequesne M**, **Malghem J**, **Dion E**. The normal hip joint space: variations in width, shape, and architecture on 223 pelvic radiographs. *Ann Rheum Dis*. 2004;63(9):1145–1151.

28. **Gallagher B**, **Tjoumakaris FP**, **Harwood MI**, **Good RP**, **Ciccotti MG**, **Freedman KB**. Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. *Am J Sports Med*. 2015;43(3):734–744.

29. **Diao N**, **Yang B**, **Yu F**. Effect of vitamin D supplementation on knee osteoarthritis: A systematic review and meta-analysis of randomized clinical trials. *Clin Biochem*. 2017;50(18):1312–1316.

30. **Gao X-R**, **Chen Y-S**, **Deng W**. The effect of vitamin D supplementation on knee osteoarthritis: A meta-analysis of randomized controlled trials. *Int J Surg*. 2017;46:14–20.

31. **Yang W**, **Sun C**, **He SQ**, **Chen JY**, **Wang Y**, **Zhuo Q**. The efficacy and safety of disease-modifying osteoarthritis drugs for knee and hip osteoarthritis-a systematic review and network meta-analysis. *J Gen Intern Med*. 2021;36(7):2085–2093.

32. **Fu S-H**, **Wang C-Y**, **Yang R-S**, **Wu F-L**, **Hsiao F-Y**. Bisphosphonate use and the risk of undergoing total knee arthroplasty in osteoporotic patients with osteoarthritis: A nationwide cohort study in Taiwan. *J Bone Joint Surg Am*. 2017;99-A(11):938–946.

33. **Davis AJ**, **Smith TO**, **Hing CB**, **Sofat N**. Are bisphosphonates effective in the treatment of osteoarthritis pain? A meta-analysis and systematic review. *PLoS One*. 2013;8(9):e72714.

34. **Bingham CO 3rd**, **Buckland-Wright JC**, **Garnero P**, **et al**. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. *Arthritis Rheum*. 2006;54(11):3494–3507.

35. **Raynauld J-P**, **Martel-Pelletier J**, **Berthiaume M-J**, **et al**. Correlation between bone lesion changes and cartilage volume loss in patients with osteoarthritis of the knee as assessed by quantitative magnetic resonance imaging over a 24-month period. *Ann Rheum Dis*. 2008;67(5):683–688.

36. **Chen C-H**, **Kang L**, **Chang L-H**, **et al**. Intra-articular low-dose parathyroid hormone (1-34) improves mobility and articular cartilage quality in a preclinical age-related knee osteoarthritis model. *Bone Joint Res*. 2021;10(8):514–525.

37. **Wang J**, **Zhou L**, **Zhang Y**, **Huang L**, **Shi Q**. Mesenchymal stem cells - a promising strategy for treating knee osteoarthritis. *Bone Joint Res*. 2020;9(10):719–728.

38. **Gertz BJ**, **Holland SD**, **Kline WF**, **Matuszewski BK**, **Porras AG**. Clinical pharmacology of alendronate sodium. *Osteoporos Int*. 1993;3 Suppl 3:S13–6.

Author information:
■ T. Kawai, MD, PhD, Assistant Professor
■ K. Nishitani, MD, PhD, Assistant Professor
■ Y. Okuzu, MD, PhD, Assistant Professor
■ K. Goto, MD, PhD, Associate Professor
■ Y. Kuroda, MD, PhD, Lecturer
■ S. Kuriyama, MD, PhD, Lecturer
■ S. Nakamura, MD, PhD, Assistant Professor
■ S. Matsuda, MD, PhD, Professor, Chair
  Department of Orthopaedic Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan.