Table 5 Prevalence (%) of coexisting disorders, such as hyperparathyroidism, osteoporosis, osteoarthritis, metabolic risk factors, and renal dysfunction, among the participants classified at the baseline by vitamin D status

	Total (N=1,683)				Men (N=595)				Women (N=1,088)			
	normal (N=295)	Vitamin D insufficiency (N=1,368)	Vitamin D deficiency (N=20)	p for trend	normal (N=164)	Vitamin D insufficiency (N=429)	Vitamin D deficiency (N=2)	p for trend	normal (N=131)	Vitamin D insufficiency (N=939)	Vitamin D deficiency (N=18)	p for trend
Hyperparathyroidism (iPTH >65 pg/mL)	6.8	8.0	45.0	<0.001*	6.1	8.2	50.0	0.057	7.6	7.9	44.4	<0.001*
Osteoporosis (L2–4)	11.5	14.1	10.0	0.442	2.4	3.7	0.0	0.712	22.9	18.9	11.1	0.376
Osteoporosis (femoral neck)	10.2	13.0	25.0	0.109	4.9	3.3	0.0	0.623	17.1	17.4	27.8	0.514
Osteoporosis (L2–4 or femoral neck)	14.6	20.5	25.0	0.057	4.9	6.3	0.0	0.758	26.9	27.1	27.8	0.997
Knee osteoarthritis (KL >=3)	19.4	20.0	35.0	0.238	15.3	14.5	0.0	0.813	24.4	22.5	38.9	0.243
Lumbar spondylosis (KL >=3)	42.7	35.9	30.0	0.072	45.1	34.5	50.0	0.054	38.7	36.5	27.8	0.568
Hypertension	67.9	70.2	60.0	0.473	71.2	76,0	100.0	0.344	63.9	67.6	55.6	0.411
Dyslipidaemia	11.5	12.5	10.0	0.855	9.8	15.6	0.0	0.156	13.7	11.1	11.1	0.667
Impaired glucose tolerance	21.3	21.5	30.0	0.653	23.2	24.7	50.0	0.648	19.1	20.0	27.8	0.688
Chronic kidney disease	43.7	42.9	40.0	0.932	46.3	42.7	0.0	0.333	40.5	43.2	44.4	0.847

iPTH intact parathyroid hormone, *L2–4* lumbar spine L2–L4, *KL* Kellgren–Lawerence grade, *BMI* body mass index

*p <0.001

significantly smaller in terms of body structure than the overall Japanese population (p <0.05) [13]. This difference should be considered when evaluating potential risk factors for men aged 70–74 years; factors such as body build, particularly greater weight, are known to be associated with metabolic risk factors and knee osteoarthritis. Therefore, our results may represent an underestimate of the prevalence of these conditions. Second, in the present study, this study was only the data of the baseline study. Thus, we were not able to confirm the causal relationship between vitamin D status and other associated factors. However, we have already completed a 3-year after follow-up study, so that we can clarify the causal relationship between vitamin D status and the above-mentioned factors in the following reports after the baseline profile of vitamin D status described in the present study. Third, the total number of individuals in the vitamin D deficiency group was very small (n=20), which could make the results pertaining to vitamin D deficiency somewhat less credible than those relating to vitamin D insufficiency. To address this limitation, we performed a multiple regression analysis using the serum levels of vitamin D as the objective variable and the identical explanatory variables as used in the multinominal regression analysis shown in Table 4. The explanatory variables were as follows: age (+1 year), gender (0: men, 1: women), regional differences (0: mountainous area, 1: coastal area), BMI (+1 kg/m^2), month of examination (0: October, November, December, 1: January), smoking (0: never, ever, 1: current), alcohol consumption (0: never, ever, 1: current), lack of regular walking outside (0: ≥5 times/week, 1: <5 times/week), regular exercise outdoors (0: yes, 1: no), serum levels of iPTH (+1 pg/mL), urinary levels of β-CTX (+1 SD), daily total energy from amount of intake (+100 Kcal/day), vitamin D (+10 μg/day), and the values of the baseline BMD at the lumbar spine (+1 SD). Supplementary Table 1 shows the lower serum levels of vitamin D were characterised by younger age, female sex, residing in a mountainous area, measurements performed in January, smoking habit, non- or ex-drinking, higher serum iPTH, and a low intake of vitamin D. This tendency was almost similar to the characteristics of vitamin D insufficiency and deficiency, with the exception that alcohol drinking was also significantly associated with lower serum levels of vitamin D. However, as shown in Table 1, the frequency of alcohol drinking was confirmed to be significantly different according to the 25D status. Thus, the results of the multinominal logistic regression did not differ substantially from those of the multiple regression analysis using continuous values for vitamin D. Rather, these results may support the characteristics of each 25D status as clarified in the present study. Finally, the nutrition survey in the present study was performed using a questionnaire with a multiple-choice style for each meal. Although this questionnaire is widely used in Japanese studies, it might raise the

possibility of recall bias. In fact, the mean dietary intake of vitamin D per day calculated in the present study tended to be high from the adequate intake (5 μg/day) published by the Ministry of Health and Welfare in Japan [37]. However, the Ministry of Health, Labour and Welfare in Japan also commented that the adequate intake had been determined as an index without enough scientific evidence. Simultaneously, this agency provided another index in which the tolerable upper intake level of vitamin D was 50 μg/day. Based on these issues regarding the estimation of vitamin D intake, we believe our results regarding the intake of vitamin D are not beyond the world consensus. Instead, the mean intake estimated in the present study could indicate that people in Japan have a much higher daily intake of vitamin D than those in most regions worldwide. Nonetheless, we were unable to conclude whether the total intake of vitamin D calculated in the present study represented actual values or was overestimated by using the questionnaire. In the other cohort from the urban area investigated in the ROAD study, we should be able to confirm the consistency of the estimation of vitamin D using the BDHQ questionnaire.

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Conflicts of interest None.

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ORIGINAL ARTICLE

The mid-term efficacy of intra-articular hyaluronic acid injections on joint structure: a nested case control study

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Abstract
Objective Intra-articular (IA) injection of hyaluronic acid (HA) has been shown to relieve osteoarthritis (OA)-related pain and improve joint structure within a 1-year period. We examined the mid-term (2-year) efficacy of IA–HA in Japanese subjects by using a large-scale population-based cohort of the Research on Osteoarthritis/Osteoporosis Against Disability study.
Methods We performed a nested case control study of 60 case control pairs matched for age (within 1 year), sex, Kellgren and Lawrence grade, and history of knee pain. The mean follow-up period after IA–HA series was 2.9 years in case patients. We examined the association of IA–HA with knee radiographic severity and knee pain. To estimate radiographic severity of OA, six distinct features—joint space area and the minimum joint space width at medial and lateral sides, osteophyte area, and tibiofemoral angle—were measured using a fully automatic computer-assisted program.
Results Comparison of the radiographic parameters between case patients and controls showed that the medial and lateral joint space areas were significantly bigger in case patients than in controls. After constructing a multivariate logistic regression model to examine the correlation of knee pain, IA–HA, and radiographic features, we found that unlike radiographic features, IA–HA was protectively associated with the presence of pain.
Conclusion IA–HA might effectively improve joint structure and relieve pain in patients with knee OA.

Keywords Hyaluronic acid · Nested case control study · Joint structure · Knee pain

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Introduction

Osteoarthritis (OA) causes cartilage degeneration and osteophyte formation in the joints and is a major contributing factor to chronic disability in the elderly in developed countries [1–3]. Changes in the lubricating properties of the synovial fluid lead to significant pain and loss of function; however, intra-articular (IA) injections of hyaluronic acid (HA), referred to as viscosupplementation, can improve the biochemical properties of the synovial fluid in joints with OA [4]. The therapeutic effects and safety of IA–HA in the treatment of OA have been demonstrated in several clinical trials [5–14], while numerous systematic reviews and meta-analyses, such as the Cochrane Review, have confirmed the efficacy of IA–HA in relieving OA-related pain and improving joint function [15–17].

On the other hand, there is insufficient evidence on the efficacy of IA–HA in improving joint structure. Potential structure-modifying effects of IA–HA in the treatment of

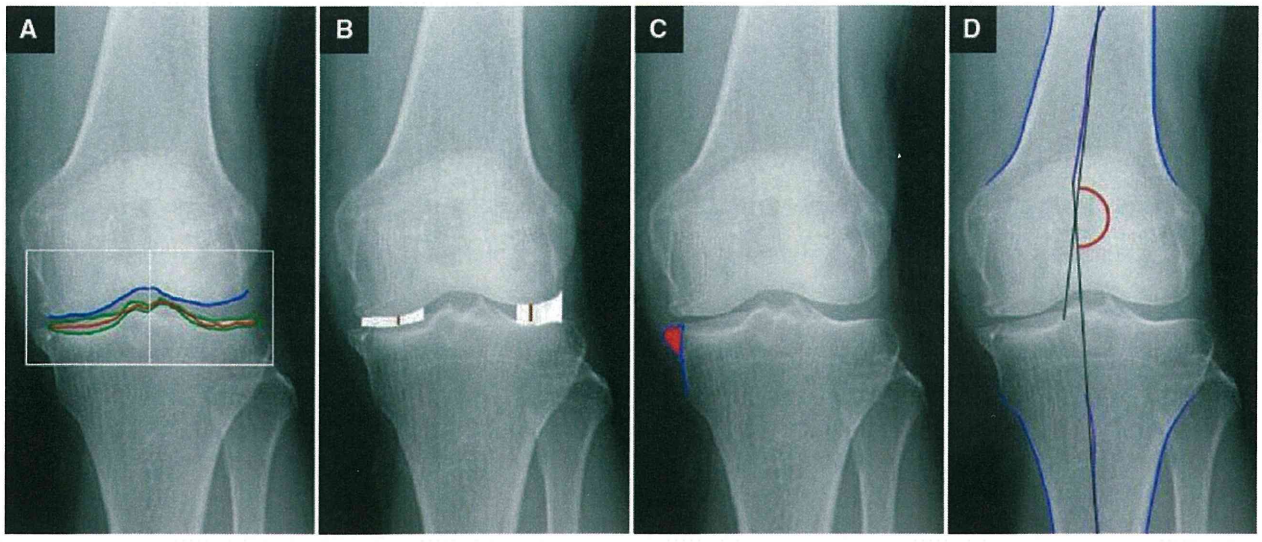

Fig. 1 Schema of image processing by KOACAD. **a** Region of interest and the center, including the tibiofemoral joint space (*white square*). Outline of the femoral condyle (*blue line*): upper and outside rims of the joint space. Outlines of the anterior and posterior margins of the tibial plateau (*green lines*) and the middle line between the two outlines (*red line*). **b** Medial and lateral joint space areas (JSAs) (*white areas*). Medial and lateral minimum joint space widths (mJSWs) (*brown lines*): the minimum vertical distances in the JSAs. **c** Osteophyte area (*red area*) that is medially prominent over the smoothly extended outline of the tibia. **d** Medial and lateral outlines (*blue lines*) of the femur and tibia from the edges of the image to the inflection points and the middle lines (*purple lines*). Tibiofemoral angle: the lateral angle between the straight regression lines (*black lines*) of the middle lines above, in the femur and tibia (color figure online)

OA have been suggested in animal models, but with conflicting results [18], and only limited studies have been performed in humans with the use of arthroscopy or plain radiography [19, 20]. Plain radiography is considered the gold standard for OA structural assessment because it is non-invasive, inexpensive, convenient, simple, and fast. However, the assessment remains limited in reproducibility and sensitivity because of the subjective judgment of individual observers and categorical classification [21–23]. Hence, in the present study, we conducted the structural assessment by obtaining the quantitative values of the major radiographic parameters of knee OA—joint space area (JSA) and minimum joint space width (mJSW) at the medial and lateral sides, osteophyte area (OPA), and tibiofemoral angle (TFA)—by using a computer-assisted measuring system (KOACAD) that we developed and reported earlier [24].

Most studies on the efficacy of IA–HA had a follow-up period within 1 year of the injection series [5–17]. Thus, the aim of the present study was to evaluate the mid-term efficacy (over 2 years) of IA–HA with regard to joint structure and pain. Since mid-term follow-up is difficult in a randomized clinical trial because of patient dropout rates, we conducted this nested case control study using a large-scale population-based cohort of the Research on Osteoarthritis/Osteoporosis Against Disability (ROAD) study [25–28].

Materials and methods

Study population

In this nested case control study, both cases and controls were selected from the participants in the baseline examination of the ROAD study. Detailed profiles have been provided elsewhere [25–28]; thus, the study population is described only briefly here. From 2005 to 2007, we created a baseline database of the clinical and genetic information of 3,040 residents of Japan (1,061 men, 1,979 women) with a mean age of 70.3 ± 11.0 years (71.0 ± 10.7 years in men and 69.9 ± 11.2 years in women). These subjects were recruited from resident registration listings in three communities with different characteristics: an urban region in Itabashi, Tokyo; a mountainous region in Hidakagawa, Wakayama; and a coastal region in Taiji, Wakayama. A detailed questionnaire consisting of 400 items was used, which included questions related to knee pain, such as "Have you experienced knee pain on most days in the past month, in addition to now?" Anthropometric measurements, including height and weight, were performed, and body mass index (BMI) was calculated for all participants.

Radiographic assessment

All participants underwent radiographic examination of both knees using an anterior-posterior view with weight-

bearing and foot map positioning. Fluoroscopic guidance with a horizontal anterior-posterior X-ray beam was used to visualize the joint space properly, and images were downloaded into Digital Imaging and Communication in Medicine (DICOM) format files. The KOACAD system has been described in detail elsewhere [24] and is summarized only briefly here. The KOACAD was programmed to measure the mJSW and JSA in the medial and lateral compartments, the OPA at the medial tibia, and the TFA using digitized knee radiographs. Initially, correction for radiographic magnification was performed based on the image size of a rectangular metal plate. Next, we undertook the determination of the region of interest (ROI), including the tibiofemoral joint space, automatically. Within the ROI, the outline of the femoral condyle was designated as the upper rim of the joint space. The two ends were determined, and vertical lines from the ends were designated as the outside rims of the joint space. Outlines of the anterior and posterior margins of the tibial plateau were drawn similarly to that of the femoral condyle, and the middle line between the two outlines was designated as the lower rim of the joint space. A straight regression line for the lower rim outline then was drawn, and the intersections of the lower rim outline and the regression line were designated as the inside rims. The medial and lateral JSAs were determined as the areas surrounded by the upper, lower, inside, and outside rims, as defined above. The medial and lateral mJSWs were further determined as the minimum vertical distances in the respective JSA. To measure the OPA and the TFA, medial and lateral outlines of the femur and tibia were drawn. Inflection points for these outlines were then calculated. The medial outline of the tibia from the inflection point was drawn upward to the joint level, and the area that was medially prominent over the smoothly extended outline was designated as the OPA. For the TFA, a line midway between the medial and lateral outlines of the femur from the top of the image to the inflection points was drawn, and the straight regression line was determined as the axis of the femur. Similarly, the straight regression line of the middle line of the tibia from the bottom to the inflection points was designated as the axis of the tibia. The lateral angle between the two axis lines was calculated as the TFA (Fig. 1). This system can quantify the major features of knee OA on standard radiographs, and it allows objective, accurate, simple, and easy assessment of the structural severity of knee OA without any manual operation in general clinical practice.

The conventional radiographic severity of OA was determined according to the Kellgren and Lawrence (K/L) grading as follows [21]: KL0, normal joint; KL1, slight osteophytes; KL2, definite osteophytes; KL3, disc-space narrowing and large osteophytes; and KL4, bone sclerosis, joint space narrowing, and large osteophytes. In the ROAD study, joints that exhibited only joint space narrowing and no large osteophytes were graded as KL3. All radiographs were examined by one experienced orthopedic surgeon (S.M.) blinded to the clinical status of the participants.

Selection of cases and controls

Cases were defined as having received IA–HA within the past 1 year. One control was randomly selected for each case from the ROAD participants, according to the following criteria: never received IA–HA, same sex, same age (within 1 year), same community, same radiographic severity (according to K/L grading), and same knee pain status. We excluded individuals with a history of intra-articular corticosteroids, rheumatoid arthritis, and knee replacement from both cases and controls.

The study was conducted with approval from the Institutional Review Boards of the University of Tokyo, and all participants provided written informed consent.

Statistical analyses

Baseline characteristics and radiographic parameters were compared between case patients and controls using the chi-square test for categorical variables and unpaired *t* test for numerical variables. For the assessment of factors associated with symptomatic knee pain, baseline characteristics and radiographic parameters were compared between knees with and without pain by chi-square test and unpaired *t* test in cases and controls, respectively. Correlations among the radiographic parameters were analyzed using Pearson's correlation test, and parameters with a correlation value of greater than 0.7 were defined as confounding factors.

Finally, we used logistic regression to test the association of knee pain status with risk and protective factors in the case control sample. Multivariable models were used to adjust for age, sex, and confounding factors. All analyses used a two-sided type I error rate of 0.05 as the threshold for statistical significance and were performed using SAS version 9.1 software (SAS Institute Inc., Cary, NC).

Results

A total of 60 cases and 60 matched controls were selected from the ROAD baseline database. The mean follow-up period after IA–HA series in cases was 2.9 (range 1–4) years.

Table 1 shows the comparison of baseline characteristics between cases and controls (Table 1). None of the characteristics, such as height, weight, BMI, knee flexion contracture, and history of non-steroidal anti-inflammatory

Table 1 Baseline characteristics of case patients and controls

Characteristic	Case patients	Controls	*P* value
Participants, no.	60	60	
Age, mean (SD), years	72.0 (8.5)	72.0 (8.5)	
Female, no. (%)	47 (78.3)	47 (78.3)	
K/L grading, no. (%)			
0	4 (6.7)	4 (6.7)	
1	10 (16.7)	10 (16.7)	
2	11 (18.3)	11 (18.3)	
3	19 (31.7)	19 (31.7)	
4	16 (26.6)	16 (26.6)	
History of knee pain, no. (%)	60 (100)	60 (100)	
Knee pain status, no. (%)	26 (43.3)	30 (50.0)	0.47
BMI, mean (SD), kg/m^2	24.5 (3.3)	24.0 (3.6)	0.37
Height, mean (SD), cm	152.7 (8.5)	152.4 (8.0)	0.84
Flexion contracture, no. (%)	22 (36.7)	19 (31.7)	0.70
Use of NSAIDs, no. (%)	60 (100)	60 (100)	1.00

BMI body mass index, *K/L* Kellgren and Lawrence, *NSAIDs* nonsteroidal anti-inflammatory drugs

drug use, was significantly different between cases and controls ($P > 0.05$) (Table 1).

To identify the radiographic factors associated with IA–HA by using the KOACAD system, we compared the radiographic parameters between case patients and controls (Table 2). We found that the medial and lateral JSAs were significantly bigger in case patients than in controls.

For the assessment of factors associated with symptomatic knee pain, baseline characteristics and radiographic parameters were compared between knees with and without pain in cases and controls, respectively (Table 3). Age was significantly higher in the group with pain than in the group without pain. Furthermore, the medial mJSW and medial JSA were significantly smaller in the group with pain than in the group without pain in cases and controls, respectively.

Although all the radiographic parameters are known to be affected as OA progresses, the changes are neither proportional nor is the relationship constant. We therefore examined the correlations among the parameters on 120 radiographs (case patients and controls) by Pearson's correlation test (Table 4). As expected, the correlation values were greater than 0.7 between the medial JSA and medial mJSW, indicating that these are confounding factors for each other.

Considering that the medial mJSW and medial JSA confound each other (Pearson's correlation value >0.7; Table 4), the medial JSA, which was significantly bigger in case patients than in controls (Table 2), was selected for the variance. Finally, we constructed a multivariate logistic regression model to examine the correlation of knee pain and the medial JSA, TFA, and IA–HA, adjusting for age and sex (Table 5). We found that IA–HA was protectively associated with the presence of pain, while the medial JSA and the TFA were not.

Discussion

Based on a present nested case–control study and the use of a fully automatic computer-assisted program, KOACAD, which can quantify the major features of knee OA on plain radiographs, the present study is the first to reveal the mid-term efficacy of IA–HA with regard to pain.

Independent measurement of the radiographic parameters by KOACAD enabled us to examine the correlation of the distinct features of OA, which might lead to a better understanding of the pathophysiology of OA. There have been no clinical trials on IA–HA that assessed the distinct features of OA; however, a randomized placebo-controlled trial that assessed joint space width has been conducted. That study showed no difference in medial femorotibial JSW narrowing between the two groups in the entire population, but among the patients with less severe disease (baseline JSW, >4.6 mm), the subgroup treated with IA–HA showed significantly less narrowing [20]. Although the authors of the study asserted that the results might be due to inaccurate and subjective measurement of the radiographs, the present KOACAD analysis has confirmed the reliability by accurate and objective measurement [24]. We matched conventional radiographic severity (K/L grading) in both the case and control groups, using the KOACAD system to the baseline data in the ROAD study, and found that the medial and lateral JSAs were associated with IA–HA

Table 2 Differences in radiographic parameters between case patients and controls

Characteristic	Case patients	Controls	*P* value
Medial JSA, mean (SD), mm^2	85.9 (5.6)	69.2 (5.5)	0.04
Lateral JSA, mean (SD), mm^2	136.3 (4.8)	112.8 (4.8)	0.0007
Medial mJSW, mean (SD), mm	2.2 (0.2)	1.9 (0.2)	0.28
Lateral mJSW, mean (SD), mm	4.1 (0.2)	4.1 (0.1)	0.84
OPA, mean (SD), mm^2	8.5 (2.5)	12.8 (2.5)	0.23
TFA, mean (SD), °	178.5 (0.7)	178.9 (0.7)	0.74

JSA joint space area, *mJSW* minimum joint space width, *OPA* osteophyte area, *TFA* tibiofemoral angle

Table 3 Baseline characteristics and radiographic parameters of case patients and controls, according to pain status

	Case patients			Controls		
	Pain (+)	Pain (−)	*P* value	Pain (+)	Pain (−)	*P* value
Characteristic						
Participants, no.	26	34		30	30	
Age, mean (SD), years	75.1 (6.0)	67.8 (9.5)	0.0006	75.2 (7.4)	68.8 (8.1)	0.002
Female, no. (%)	18 (69.2)	29 (85.3)	0.21	27 (90.0)	20 (33.3)	0.06
BMI, mean (SD), kg/m^2	25.0 (3.2)	24.0 (3.4)	0.26	24.5 (3.6)	23.4 (3.6)	0.21
Flexion contracture, no. (%)	9 (34.6)	13 (38.2)	0.86	13 (43.3)	6 (20.0)	0.09
Radiographic parameter						
Medial JSA, mean (SD), mm^2	70.9 (7.6)	105.5 (8.9)	0.005	51.9 (6.3)	85.9 (6.1)	0.0003
Lateral JSA, mean (SD), mm^2	132.6 (7.1)	141.2 (8.1)	0.43	110.4 (6.0)	115.2 (5.9)	0.57
Medial mJSW, mean (SD), mm	1.7 (0.2)	2.7 (0.3)	0.007	1.3 (0.2)	2.6 (0.2)	<0.0001
Lateral mJSW, mean (SD), mm	4.0 (0.2)	4.3 (0.3)	0.5	3.9 (0.2)	4.2 (0.2)	0.22
OPA, mean (SD), mm^2	12.7 (3.4)	4.6 (3.3)	0.09	18.6 (3.1)	5.3 (3.5)	0.07
TFA, mean (SD), °	180.4 (1.0)	176.1 (1.1)	0.007	180.7 (0.9)	177.0 (0.9)	0.006

JSA joint space area, *mJSW* minimum joint space width, *OPA* osteophyte area, *TFA* tibiofemoral angle

Table 4 Correlations among radiographic parameters

	Medial JSA	Lateral JSA	Medial mJSW	Lateral mJSW	OPA	TFA
Medial JSA	1.00					
Lateral JSA	0.14 (0.12)	1.00				
Medial mJSW	0.90 (<0.0001)	0.13 (0.78)	1.00			
Lateral mJSW	0.21 (0.02)	0.63 (<0.0001)	0.19 (0.04)	1.00		
OPA	−0.36 (<0.0001)	0.23 (0.01)	−0.37 (<0.0001)	0.03 (0.97)	1.00	
TFA	−0.53 (<0.0001)	0.14 (0.0004)	−0.49 (<0.0001)	−0.16 (0.12)	0.45 (<0.0001)	1.00

Data are expressed as Pearson's correlation values with *P* values in parentheses

JSA joint space area, *mJSW* minimum joint space width, *OPA* osteophyte area, *TFA* tibiofemoral angle

Table 5 Multivariate logistic regression analysis for odds ratio (OR) and 95 % confidence interval (CI) of the risk and protective factors for knee pain

	OR for pain	95 % CI	*P* value
Medial JSA	1.00	0.99–1.02	0.18
TFA	0.94	0.86–1.04	0.28
IA–HA	0.25	0.10–0.59	0.00

IA–HA intra-articular hyaluronic acid, *JSA* joint space area, *TFA* tibiofemoral angle

treatment but that the mJSW and osteophyte formation were not. However, the amount of left cartilage depends on not only by the effect of HA but also by the X-ray reading; hence, these results could be affected by the variance of K/L grading.

This result has been demonstrated in in vitro studies, which have shown that Fas-induced apoptosis of chondrocytes in patients with OA is suppressed by IA–HA [29]. The anti-apoptotic effect of IA–HA is mediated by its binding to specific receptors, CD44 and ICAM, suggesting that HA may decrease the progression of chondrocyte apoptosis in OA, subsequently protecting knee cartilage.

Arthritis is the most common cause of pain in the elderly [30], and knee pain is the principal clinical symptom of knee OA. Although much effort has been devoted toward a definition of knee pain, its correlation with the radiographic severity of knee OA is not as strong as one would expect [31–33]. Hence, this study sought to identify the clinical and radiographic factors related to knee pain in OA, and we revealed that IA–HA was protectively associated with the presence of pain; however, no radiographic feature was associated with the presence of pain, after adjusting for age, sex, and confounding. This result indicates that IA–HA treatment was more strongly associated with the presence of pain than radiographic features. The effects of treatment include not only cartilage protection but also improved joint lubrication, synovial fluid viscosity, and analgesic and anti-inflammatory effects [34–37].

There are several limitations to the present study. First, this is a cross-sectional study on factors associated with IA–HA treatment; thus, a causal relationship with radiographic features and clinical conditions could not be determined. However, such data as the quantitative values of the major radiographic parameters of knee OA were analyzed as the structural assessment; therefore, ample evidence on the background of IA–HA treatment could be obtained. Second, clinical information was obtained by interviews of orthopedic surgeons; thus, there is a possibility that both self-selection bias and recall bias may have occurred. Third, there are several HA products of different molecular weight available for injection [38]; however, we could not specify the categories, e.g., low molecular weight or high molecular weight products, in the present study. Furthermore, the follow-up period after IA–HA series was unequal (mean 3 years, range 1–4 years); therefore, our results could be affected by the variance of follow-up period.

In conclusion, a preliminary nested case control study and KOACAD revealed that the medial and lateral JSA were associated with IA–HA treatment but that the mJSW and osteophyte formation were not. We also determined that IA–HA treatment was protectively associated with the presence of pain; however, no radiographic feature was associated with the presence of pain, after adjusting for age, sex, and confounding. Further studies, along with longitudinal data from the ROAD study, will elucidate the environmental background of IA–HA efficacy in the treatment of OA and help clarify clinical evidence for the development of other disease-modifying treatments.

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Conflict of interest None.

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