Quantitative Radiographic Features of Early Knee Osteoarthritis: Development Over 5 Years and Relationship with Symptoms in the CHECK Cohort

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ABSTRACT. ***Objective.*** To evaluate whether computer-assisted, interactive digital analysis of knee radiographs enables identification of different quantitative features of joint damage, and to evaluate the relationship of such features with each other and with clinical characteristics during 5-year followup in early osteoarthritis (OA).

Methods. Knee radiographs from the Cohort Hip and Cohort Knee (CHECK) study, including 1002 individuals with early OA complaints, were evaluated for different measures with knee images digital analysis (KIDA). To aid definition of different radiographic features of OA, principal component analysis of KIDA was used. Features were correlated (Pearson) to each other, evaluated for changes over time, and related to clinical outcome (Western Ontario and McMaster Universities Osteoarthritis Index for pain and function) using baseline, 2-year, and 5-year followup data.

Results. The identified radiographic features were joint space width (JSW: minimum, medial, lateral), varus angle, osteophyte area, eminence height, and bone density. The features progressed in severity at different times during followup: early (medial JSW, osteophyte area), late (minimum and lateral JSW, eminence height), and both early and late (varus angle, bone density). Correlations between different radiographic features varied between timepoints. The JSW features were most strongly related to each other (largest r = 0.82), but also, e.g., osteophytes and bone density were correlated (largest r = 0.33). The relationships with clinical outcome varied over time, but were most commonly found for osteophyte area and JSW.

Conclusion. In this early OA cohort, different radiographic features were identified that progressed at different rates between timepoints. The relations between radiographic features and with clinical outcome varied over time. This implies that longitudinal evaluation of different features can improve insight into progression of OA. (J Rheumatol First Release Nov 1 2012; doi:10.3899/jrheum.120320)

Key Indexing Terms:
KNEE JOINT OSTEOARTHRITIS RADIOGRAPHY

Osteoarthritis (OA) is the most common joint disorder[1], characterized by pain, functional disability, and limited quality of life. Structural changes affect the whole joint and comprise cartilage damage, osteophyte formation, changes in subchondral bone density, synovial inflammation, and involvement of soft tissue (such as ligaments and muscles)[2]. Diagnosis of OA, especially in an early phase of the disease, is difficult because of the lack of sensitive and specific diagnostic criteria[3,4]. The inconsistent association that is commonly found between clinical symptoms and radiographic characteristics representing structural damage hampers definition of such criteria[5,6,7]. The detection of an association might be improved by measuring different features of radiographic OA. Evaluation of different features over time, from a very early phase of the disease, might provide more insight into the development and progression of structural damage. For example, the detailed evaluation of such features might reveal a sequence in the development of specific radiographic aspects during the course of the disease, and the existence of specific relationships between aspects of radiographic damage over time.

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Knee images digital analysis (KIDA)[8,9,10] has been developed to measure radiographic OA damage of the knee in more detail on a continuous scale (quantitative), in contrast to the existing ordinal methods such as Kellgren and Lawrence (K&L) grading[11] and the Altman atlas[12]. The use of KIDA measurement aims at valid and sensitive evaluation of OA progression for application in clinical studies. For evaluation of the onset and progression of OA, it is important to investigate whether specific changes in specific radiographic features can be identified using the KIDA measurements. The aim of our study was to evaluate radiographic OA development over time from an early phase of the disease using specific radiographic features based on KIDA measurements, and to evaluate how these features relate to each other and to clinical characteristics of OA.

MATERIALS AND METHODS

Cohort Hip and Cohort Knee (CHECK). The CHECK study is a prospective 10-year followup OA study in 10 participating hospitals in The Netherlands, initiated by the Dutch Arthritis Association. Individuals (n = 1002) with pain and/or stiffness of hip and/or knee, age 45–65 years, and without a previous visit or with a first visit no longer than 6 months before to a general practitioner for these complaints were included in the cohort[13]. The study procedures are in accord with the standards of the medical ethics committees of all 10 participating hospitals, and all participants gave their written informed consent.

The course of complaints and radiographic damage was monitored to identify markers for diagnosis and progression of disease. Study data were used from baseline (T0), 2-year followup (T2y), and 5-year followup (T5y).

Clinical characteristics. In CHECK, clinical characteristics of OA are collected yearly by use of questionnaires and physical examination. Clinical OA at the joint level was expressed by the presence of pain during examination of joint motion by the physician, for the left and right knee separately. To express clinical OA at the participant level, the pain and functional limitation scores of the Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) were used.

Radiographic characteristics. In CHECK, posteroanterior weight-bearing semiflexed views are acquired without fluoroscopy according to a standardized protocol (Buckland-Wright)[14,15]. In our study, the different radiographs of both knees acquired at T0, T2y, and T5y were evaluated. By use of KIDA, 14 different radiographic measurements were quantitatively taken in predefined areas (Figure 1), as described extensively by Marijnissen, *et al*[8] and Kinds, *et al*[10].

Minimum joint space width (JSW in mm) was measured as the smallest distance between femur and tibia. Medial JSW and lateral JSW were defined as the mean of 4 predefined locations in each compartment. The varus angle (in degrees) between the femur and tibia was determined in the frontal plane using the intersection points that determine the bone and cartilage interface; a positive value represents (more) varus and a negative value represents valgus alignment. Height of the lateral and medial tibial eminence was measured in mm. Osteophyte area (in mm^2) was determined at the lateral and medial femur and lateral and medial tibia. Bone density (in mmAl equivalents; as a measure for subchondral sclerosis) was determined at 4 predefined locations in the lateral and medial femur and tibia, by normalizing the gray values of the subchondral bone region to those of an aluminum reference step wedge that was present on all radiographs[16]. The KIDA measurements were performed in random order by an experienced observer (ML) blinded to individual and disease characteristics and timepoint of evaluation. The intraobserver variation tested by random reanalysis of 108 radiographs several months later revealed good intraobserver variability (ICC = 0.73–0.99) for the different measurements. The number of analyzed knees may vary slightly for each of the radiographic measurements because KIDA measurement can be hampered by poor radiographic quality, despite standardized procedures. For example, the osteophyte area cannot always be thoroughly outlined, and bone density measurement requires good contrast and a clearly visible aluminum reference wedge.

Identification of different radiographic features. Principal component analyses were performed to help determine how the 14 KIDA measurements can best be reduced into a smaller set of components that represent specific separate radiographic OA characteristics. With these analyses, structure in the relationships between the 14 measurements is explored to identify underlying domains. In our analysis the number of extracted components was determined using the Kaiser criterion (extracting only factors with "eigenvalues" > 1), and using an Equamax rotation matrix of the factor loadings[17]. Specific radiographic features were then defined based on the result of these analyses and discussion with experts (FL, AM).

KIDA measurements were available for 1713 of 2004 knees (demographics, clinical characteristics, and K&L grades were not statistically significantly different between participants with and those without KIDA measurements). At T0 and T5y, five similar components were identified. At T2y, two components were identified, but when the number of components was forced to 5, the definition of components was similar to the other timepoints. Table 1 shows the rotated component matrix at T5y.

The 5 extracted components could be labeled as medial JSW, lateral JSW, osteophyte (area), eminence (height), and bone density. In the medial JSW component, the factor loading for minimum JSW was considerable, and in the lateral JSW component, the factor loading for varus angle was considerable. Since the minimum JSW is commonly reported as a separate measure for OA severity[18,19], which we considered important, minimum JSW was chosen as an additional radiographic feature. Varus angle has a different measurement unit (degrees) than the other features, and was therefore considered an important feature as well. In the components in which more KIDA measurements were combined, i.e., defined as osteophyte area, eminence, and bone density, the factor loadings of the most prominent measurements were of comparable magnitude. Hence, the radiographic features were defined as follows (enabling straightforward interpretation of radiographic OA features in clinical practice): (1) minimum JSW (mm), value as measured by KIDA; (2) medial JSW (mm), value as measured by KIDA; (3) lateral JSW (mm), value as measured by KIDA; (4) varus angle (degrees), value as measured by KIDA (+: varus and –: valgus); (5) osteophyte area (mm^2), sum of lateral and medial femur, and lateral and medial tibia; (6) eminence height (mm), sum of lateral and medial eminence height; and (7) bone density (mmAl), mean of lateral and medial femur, and lateral and medial tibia.

The number of knee radiographs available for determination of the radiographic features differed for the 3 timepoints: at T0, 922 left knees and 929 right knees; at T2y, 920 left and 913 right knees; and at T5y, 859 left and 854 right knees.

Statistical analysis. The development of the radiographic features over time (T0, T2y, and T5y) was described separately for left and right knees. This is because measurements in the same participant are not independent, and also there might be a difference in progression between the left and right knees.

To investigate the relationship between the radiographic features and to evaluate whether a specific time sequence of development exists, a correlation matrix was calculated. Pearson correlations were determined between radiographic features at T0, T2y, and T5y at the same timepoint (concurrently) but also with time lags (nonconcurrent) between the features (e.g., JSW at T0 and osteophyte area at T2y).

Cross-sectional univariate and multivariate regression analyses were used to study the relationship of the radiographic features with clinical outcome (pain presence, WOMAC pain, and function score) at T0, T2y, and T5y (dependent variable). A manual backward stepwise selection procedure was used to arrive at a final model. In addition to radiographic features, demographic and clinical characteristics that were possibly associated with

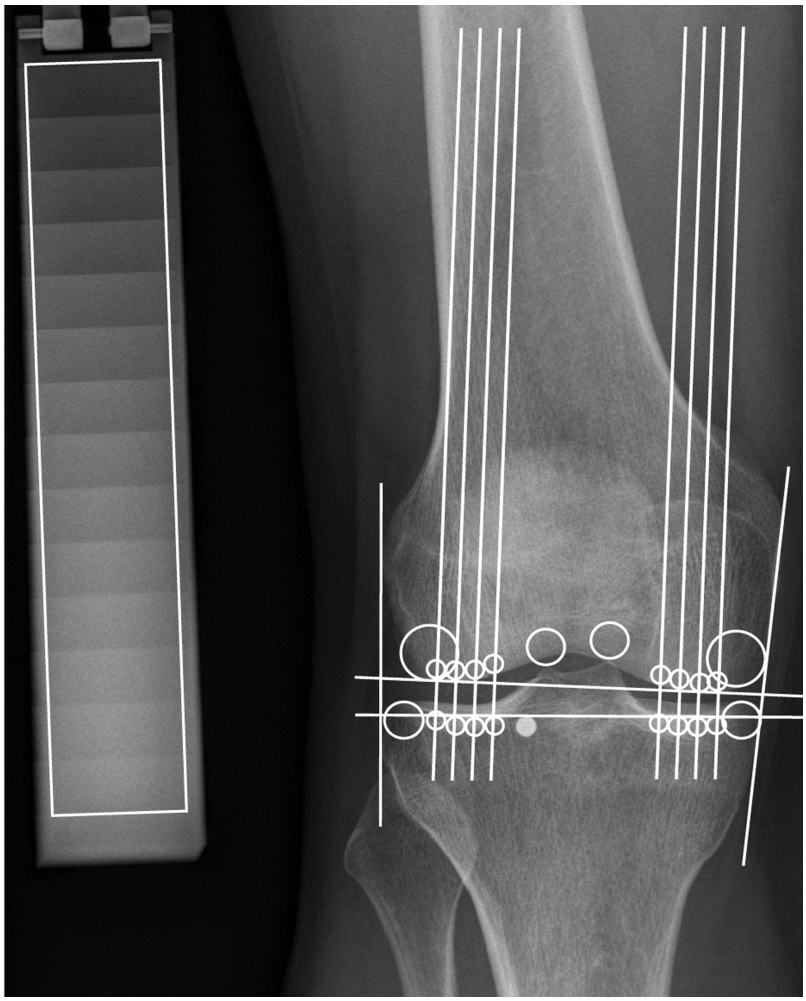

Figure 1. An image from knee images digital analysis (KIDA). The framework determines the joint dimensions, the smaller circles are used for joint space width and bone density evaluation in the lateral and medial femur and tibia, the medium circles are placed on top of the lateral and medial eminence, and the larger circles are used for osteophyte area measurement in the lateral and medial femur and tibia.

Table 1. Principal component analysis: rotated component matrix at 5-year followup. Factor loading per knee images digital analysis (KIDA) measurement is given for 5 components. Identified components are in bold type.

KIDA Measurements	Components				
	Medial JSW	Lateral JSW	Osteophyte	Eminence	Bone Density
Minimum JSW	**0.85**	–0.08	–0.11	–0.24	–0.05
Medial JSW	**0.90**	–0.13	–0.08	0.18	0.06
Lateral JSW	0.09	**0.93**	–0.01	0.26	0.05
Varus angle	–0.47	**0.86**	0.05	0.08	–0.02
Osteophyte femur lateral	–0.05	0.32	**0.60**	0.02	0.10
Osteophyte femur medial	–0.34	–0.01	**0.56**	0.05	0.06
Osteophyte tibia lateral	0.02	–0.08	**0.73**	0.27	0.00
Osteophyte tibia medial	–0.09	–0.01	**0.77**	–0.05	0.03
Eminence height lateral	–0.09	0.18	0.10	**0.86**	0.05
Eminence height medial	0.03	0.12	0.03	**0.86**	0.11
Bone density femur lateral	0.05	0.08	0.04	0.17	**0.93**
Bone density femur medial	–0.16	0.09	0.06	0.11	**0.93**
Bone density tibia lateral	0.14	–0.11	0.08	0.07	**0.93**
Bone density tibia medial	–0.06	0.07	0.07	–0.01	**0.96**

JSW: joint space width; osteophyte: osteophyte area; eminence: eminence height.

clinical outcome were evaluated. These comprised age, sex, and erythrocyte sedimentation rate (ESR, in mm/h) at T0, and body mass index (BMI, in kg/m^2) at the evaluated timepoint (T0, T2y, and T5y). ESR was included because it is frequently determined in this early stage of OA to identify arthritic conditions. Analyses were performed both at the level of the joint and at the level of the participant.

On the joint level, the dependent variable was the presence (1) or absence (0) of pain in a specific knee (left or right). The features were evaluated as the measured (calculated) value for each knee, and also as the difference between a knee and the contralateral knee of a participant (to take into account that the absolute value of the radiographic features might partly be a characteristic of the individual)[9]. In the T2y and T5y analyses, the presence at baseline of a painful joint was also evaluated as a potential confounder regarding the outcome. The analysis with presence of pain as outcome was performed by logistic regression in which the dependency of the left and right knee within individuals was taken into account, using Generalized Linear Mixed Model regression analysis with a random intercept [PROC GLIMMIX in Statistical Analysis System (SAS)].

On the participant level, the dependent variables were the WOMAC pain and functional limitation scores. The radiographic features comprised the sum of the left and right knee per participant (to represent the total burden of the radiographic features), and also the absolute difference between the left and right knee[9]. To reduce potential confounding by OA in other joints, this regression analysis was performed in a subgroup of participants with only involvement of the knees; participants with pain or radiographic involvement (defined as K&L grade ≥ II) in the hip at T0 were excluded.

Analyses were performed using SPSS (Statistical Package for the Social Sciences) version 15.0 and SAS version 9.1.3. A p value < 0.05 was considered statistically significant.

RESULTS

All 1002 CHECK participants were evaluated. Most participants in CHECK were female (79%) with mean age (± SD) 56 ± 5 years and ESR 8 mm/h (5–13; median and 25-75th percentile) at T0. Median BMI was 26 (23–28) at T0, 25 (23–28) at T2y, and 26 (23–28) at T5y. The symptoms did not evidently increase during followup, but remained the same or improved slightly. The median WOMAC pain score (0–100 scale, with 100 being worst condition) was 25 (10–35) at T0, 20 (10–35) at T2y, and 20 (5–35) at T5y. The WOMAC function score was 21 (10–35), 19 (7–32), and 21 (9–37) at T0, T2y, and T5y, respectively. At inclusion, 41% of the participants had pain in the knee(s) only, 42% had pain in the knee(s) and hip(s), and 17% had hip pain only. On the joint level, knee pain was present in 65% of 2004 knees (left and right of 1002 participants) at T0, in 56% at T2y, and in 51% at T5y. The K&L grade at T0 was 0 in 81%, I in 16%, II in 3%, and III in 0.4% of knees.

Development over time of different radiographic features. Overall, during followup the knees with early signs of OA in CHECK revealed a statistically significant increase in radiographic severity of OA between T0 and T2y as well as between T2y and T5y on all radiographic features (Figure 2). Only the changes between T0 and T2y in minimum JSW and the increase in eminence height in the left knees were not statistically significant. Changes in medial JSW and osteophyte area were most evident between T0 and T2y. In contrast, changes in minimum JSW, lateral JSW, and eminence height were most evident between T2y and T5y. Varus angle (and bone density) showed changes during both followup periods.

Relation between different radiographic features. The 7 radiographic features were commonly significantly correlated, both at concurrent and nonconcurrent timepoints (Table 2 gives results for the right knees; these were similar to results for the left knees). The correlations discussed are statistically significant unless stated otherwise.

The correlations were commonly strongest at the same timepoint (concurrently), and concurrent correlations often increased over time: e.g., the correlation of varus angle with minimum as well as medial JSW, and the correlations between eminence height and minimum as well as lateral JSW. The concurrent correlations were more significant between the 3 JSW measurements (minimum, medial, and lateral) and varus angle (largest r between varus angle and lateral JSW is 0.82, medial JSW is –0.56, and minimum JSW is –0.46) than between these 4 features and the 3 other radiographic features (osteophyte area, eminence height, and bone density). Still, considerable correlations were found between lateral JSW and osteophyte area, eminence height, and bone density. The osteophyte area was most strongly related to bone density and was correlated to eminence height, lateral JSW, and varus angle with comparable strength.

At nonconcurrent timepoints the correlations were significant but were generally weaker than at concurrent timepoints. Interestingly, the minimum JSW at T5y correlated more strongly with the osteophyte area (r values around –0.15) than the minimum JSW at the other timepoints (r values mostly not significant), irrespective of the timepoint of the osteophyte area. Further, the correlation between eminence height and osteophyte area was strongest when eminence height was measured at T5y and osteophyte area was measured at T0 (r = 0.25), and this correlation decreased over time (r = 0.16 when osteophyte area was measured at T5y). This is also considered to be in accord with the development of osteophytes before eminence height (Figure 2).

Relationship of different radiographic features with clinical outcome. Osteophyte area and JSW features were associated with the presence of knee pain at all 3 timepoints (Table 3). Interestingly, the model at T0, but not at T2y and T5y, mainly included the difference between the contralateral knees for the radiographic features, although associations were sometimes counterintuitive. Pain at T0 was a prominent predictor for a painful knee at T2y and T5y, together with specific radiographic features.

In the multivariate analyses of the subset of 336 participants with only knee pain and no hip involvement at T0, only a few radiographic features were found to be associated with WOMAC pain score (Table 4A). Again, early in the disease (at T0 and T2y), the models included differences between the contralateral knees in radiographic features (and no sum scores of the radiographic features), with a

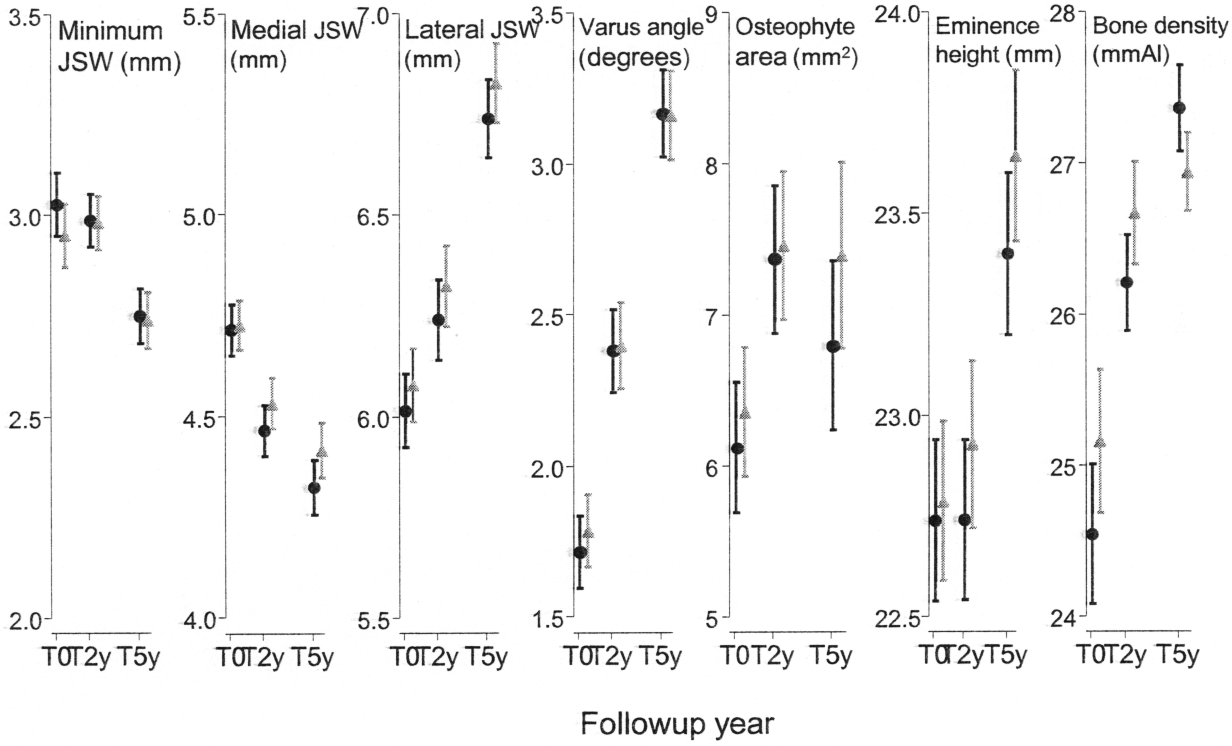

Figure 2. Mean values for separate radiographic features (95% CI) at baseline (T0), 2-year followup (T2y), and 5-year followup (T5y) for left knees (black dots) and right knees (gray triangles). JSW: joint space width.

larger difference representing more pain. At T5y, sum scores of the radiographic features were included in the model: smaller minimum JSW (sum) and larger osteophyte area (sum) were associated with more pain.

Also, few radiographic features were associated with WOMAC function score (Table 4B). Osteophyte area was associated with WOMAC function at all timepoints. At T0 and T5y the sum of the osteophyte area was associated with WOMAC function, but unexpectedly at T2y a higher difference in osteophyte area was related to less functional disability. Next to the osteophyte area, at T0 the difference in bone density was associated with WOMAC function. At T5y also the sum of the minimum JSW, a feature that was found to progress later in the disease (Figure 2), was associated with outcome. Residuals of all final multivariate regression modes were normally distributed.

DISCUSSION

In this cohort of participants with very early symptoms related to OA, radiographic features were defined as minimum JSW, medial JSW, lateral JSW, varus angle, osteophyte area, eminence height, and bone density. These features were related to each other and partly to clinical outcome (pain presence and WOMAC pain and function score). The relationship between these radiographic features and the relationship of these features with clinical outcome were found to change during progression of disease.

Measurement of JSW is already common in evaluating radiographic OA (progression)[18,20,21], and has been used to evaluate the relationship between radiographic and clinical OA characteristics[22,23]. Although the measurement of osteophytes and joint angle has been described[24], the application of such measures in a clinical study has not been reported. Moreover, these measures are commonly used in established OA (e.g., K&L grade ≥ II)[25,26] and not in (very) early OA.

The decrease over time in minimum JSW and medial JSW is considered to be in accordance with the increase in lateral JSW and varus angle. The early progression of medial JSW and osteophyte area (between T0 and T2y) in the participants with early (symptoms of) OA is in agreement with the assumed sequence of these features in K&L grading. However, in our study varus angle and bone density showed promise as early markers of radiographic damage as well.

The surplus value of measuring quantitative radiographic features is expected to be even larger when standardization of radiographic acquisition can be improved. Currently, when radiographic progression is only subtle, reliability of measurement of OA features such as JSW is influenced by variation in positioning of the knee[27]. It should be acknowledged that 3-D imaging modalities [e.g., magnetic resonance imaging (MRI) or computed tomography] have certain advantages over plain radiography. Irrespectively, optimization of evaluation of plain radiographs and the

Table 2. Matrix of Pearson correlation coefficients (r) between radiographic features of right knees at baseline (T0), 2-year followup (T2y), and 5-year followup (T5y). Statistically significant data are in bold type.

	Minimum JSW			Medial JSW			Lateral JSW			Varus Angle			Osteophyte Area			Eminence Height			Bone Density		
	T0	T2y	T5y	T0	T2y	T5y	T0	T2y	T5y	T0	T2y	T5y	T0	T2y	T5y	T0	T2y	T5y	T0	T2y	T5y
Minimum JSW																					
T0	1	**0.49**	**0.49**	**0.48**	**0.36**	**0.36**	**0.10**	–0.04	–0.02	**–0.22**	**–0.22**	**–0.22**	0.04	**–0.10**	0.03	**0.11**	**–0.11**	**–0.11**	**–0.22***	**–0.09**	0.05
T2y		1	**0.61**	**0.48**	**0.60**	**0.52**	**0.16***	0.02	–0.01	**–0.16**	**–0.30**	**–0.31**	–0.01	0.03	**–0.09**	0.01	**–0.16**	**–0.12**	–0.04	–0.01	0.06
T5y			1	**0.44**	**0.52**	**0.62***	0.05	–0.04	**–0.13**	**–0.23**	**–0.33**	**–0.46***	**–0.15***	**–0.16***	**–0.15**	–0.03	**–0.12**	**–0.25***	**–0.14**	–0.05	**–0.10**
Medial JSW																					
T0				1	**0.75**	**0.71**	**0.27***	**0.08**	**0.08**	**–0.38**	**–0.35**	**–0.35**	0.02	0.02	0.00	**0.18***	0.03	0.06	–0.04	0.05	**0.08**
T2y					1	**0.80**	**0.23**	**0.12**	0.06	**–0.26**	**–0.44**	**–0.42**	–0.01	–0.06	**–0.10**	**0.14**	0.06	0.04	0.06	0.06	**0.07**
T5y						1	**0.20**	**0.09**	0.03	**–0.25**	**–0.36**	**–0.56***	0.00	–0.01	**–0.10***	**0.14**	0.06	0.06	0.05	**0.09***	0.03
Lateral JSW																					
T0							1	**0.48**	**0.40**	**0.76**	**0.29**	**0.18**	**0.15**	**0.11**	**0.10**	**0.31**	**0.11**	**0.14**	**0.14**	**0.12**	**0.10**
T2y								1	**0.49**	**0.39**	**0.82***	**0.32**	**0.21***	**0.17**	**0.16**	**0.15**	**0.36**	**0.23**	**0.19**	**0.22***	**0.13**
T5y									1	**0.32**	**0.39**	**0.79**	**0.17**	**0.12**	**0.14**	**0.07**	**0.14**	**0.39***	**0.13**	**0.10**	**0.10**
Varus angle																					
T0										1	**0.50**	**0.40**	**0.13**	**0.09**	**0.09**	**0.16**	0.06	**0.08**	**0.13**	0.07	0.01
T2y											1	**0.54**	**0.19***	**0.17**	**0.19**	0.03	**0.26***	**0.16**	**0.11**	**0.14***	0.05
T5y												1	**0.13**	**0.10**	**0.17**	–0.06	0.05	**0.25**	0.04	0.01	0.04
Osteophyte area																					
T0													1	**0.58**	**0.60**	**0.13**	**0.18**	**0.25***	**0.21**	**0.21**	**0.18**
T2y														1	**0.60**	**0.09**	**0.09**	**0.18**	**0.30**	**0.33***	**0.22**
T5y															1	**0.09**	**0.13**	**0.16**	0.03	**0.08**	**0.15**
Eminence height																					
T0																1	**0.71**	**0.66**	0.06	**0.15**	**0.16**
T2y																	1	**0.73**	**0.10**	**0.20***	**0.17**
T5y																		1	**0.18**	**0.18**	**0.18**
Bone density																					
T0																			1	**0.43**	**0.33**
T2y																				1	**0.54**
T5y																					1

* Strongest correlations between radiographic features. JSW: joint space width.

optimal use of radiography remain of value as long as MRI is not the standard in regular care.

Radiographic joint damage is represented by a smaller minimum and medial JSW, and larger lateral JSW and varus angle (Figure 1) because of primary medial compartment narrowing and subsequent lateral compartment widening. Thus the negative correlations between minimum/medial JSW and lateral JSW/varus angle were expected, as were the positive relations between minimal and medial JSW and between lateral JSW and varus angle. However, the positive correlation between the medial and lateral JSW was not expected, but decreased over time (concurrent r = 0.27 at T0, 0.12 at T2y, and not significant at T5y). This is also considered to be in accord with the development of osteophytes before eminence height (Figure 2).

Interestingly, widening of the lateral joint space was identified as a characteristic of progression of early radiographic OA, especially between T2y and T5y. The current focus in clinical trials on narrowing of the medial joint space only, which is the most commonly affected compartment in OA, may be supported by relevant information regarding widening of the lateral joint space.

Further, our study showed that osteophyte development (despite the limitation of evaluation in a 2-D plane) occurred in the early phase, in contrast to cartilage loss, which is in accord with the general development of the radiographic features over time (Figure 2).

The value of bone density on radiographs, as a surrogate measure of sclerosis, may need reappraisal. In the Altman atlas[12], bone density is scored roughly as either present or absent for different joint compartments. However, our results showed a gradual increase in bone density over time. Grading bone density on more levels, as is the case for joint space narrowing in the Altman atlas (0–3 scale instead of absent-present), could lead to improvement of grading of radiographic OA severity.

While all features showed increased radiographic severity, the symptoms did not simultaneously and consistently increase during followup. Although the detection of an association between radiographic and clinical characteristics is difficult[5,7], specific radiographic features were found to be associated with clinical outcome in (very) early OA. The finding that fewer radiographic features were significantly associated with WOMAC scores than with knee pain might be due to the evaluation on the participant level instead of the joint level and on the insensitivity of the

Table 3. Multivariate regression analyses at baseline (T0), 2-year followup (T2y), and 5-year followup (T5y) with presence of knee pain as dependent variable. Difference refers to knee and contralateral knee. Results are based on generalized linear mixed model regression analysis with a random intercept, taking into account the dependency of knees (the unit of analysis) within individuals.

	OR (95% CI)	p
Radiographic feature T0		
Minimum JSW (difference)	0.81 (0.71, 0.91)	0.001
Osteophyte area	1.43 (1.09, 1.88)	0.01
Medial JSW (difference)	0.70 (0.49, 1.00)	0.05
Lateral JSW (difference)	1.38 (0.99, 1.94)	0.06
Varus angle (difference)	0.74 (0.57, 0.96)	0.02
Eminence height (difference)	1.08 (1.02, 1.13)	0.007
Demographic		
ESR T0	1.02 (1.01, 1.04)	0.006
Radiographic feature T2y		
Lateral JSW	0.87 (0.76, 0.99)	0.04
Varus angle	1.17 (1.06, 1.29)	0.002
Osteophyte area	1.42 (1.06, 1.91)	0.02
Demographic and clinical		
Pain presence T0	4.53 (3.57, 5.75)	< 0.0001
Radiographic feature T5y		
Minimum JSW	0.79 (0.70, 0.90)	0.0004
Osteophyte area	1.47 (1.08, 2.01)	0.02
Bone density	1.04 (1.00, 1.07)	0.04
Demographic and clinical		
Female T0	1.57 (1.11, 2.21)	0.01
BMI T5y	1.04 (1.01, 1.07)	0.01
Pain presence T0	2.68 (2.09, 3.43)	< 0.0001

JSW: joint space width; ESR: erythrocyte sedimentation rate; BMI: body mass index.

WOMAC score at the individual level. When studying clinical OA at the joint level, the association is studied more directly, with less interference of other (systemic) factors. The association of the differences between the contralateral knees in radiographic features with clinical outcome early, but not later on in the disease could suggest that this difference in radiographic features between knees in an individual is a very sensitive measure in the early phase of the disease, in which only 1 of the knee joints is commonly affected. However, the regression analyses sometimes showed counterintuitive associations, because smaller differences in features were also found to be associated with worse clinical outcome. Therefore, the interpretation of these differences needs further evaluation.

Osteophyte area was commonly identified as a feature of radiographic OA that was associated with clinical outcome, but this was not consistent for the other radiographic features. The importance of these other features appears limited or might depend on the phase of the disease regarding clinical outcome.

Moreover, several subtypes or phenotypes of OA might exist with specific combinations of (progression in) radiographic features and clinical outcome in subgroups of individuals. In our study, participants might be affected differently, and studying this group as a whole might have hampered the detection of an association of specific radiographic features with clinical outcome[1]. Specific pheno-

Table 4A. Multivariate linear regression analyses at baseline (T0), 2-year followup (T2y), and 5-year followup (T5y) with WOMAC pain (0–100 scale) as dependent variable. Difference refers to knee and contralateral knee and sum to left + right knee.

	ß (95% CI)	p
Radiographic feature T0		
Medial JSW (difference)	4.36 (1.26, 7.45)	0.01
Demographic		
BMI T0	0.80 (0.35, 1.25)	0.0006
Radiographic feature T2y		
Bone density (difference)	1.14 (0.21, 2.07)	0.02
Demographic		
BMI T2y	0.79 (0.31, 1.26)	0.001
ESR T0	0.34 (0.05, 0.62)	0.02
Radiographic feature T5y		
Minimum JSW (sum)	–1.28 (–2.26, –0.29)	0.01
Osteophyte area (sum)	3.49 (0.73, 6.24)	0.01
Demographic		
BMI T5y	0.81 (0.39, 1.23)	0.0002

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index for pain; ß: regression coefficient; JSW: joint space width; BMI: body mass index; ESR: erythrocyte sedimentation rate.

Table 4B. Multivariate linear regression analyses at baseline (T0), 2-year followup (T2y), and 5-year followup (T5y) with WOMAC function (0–100 scale) as dependent variable. Difference refers to knee and contralateral knee and sum to left + right knee.

	ß (95% CI)	p
Radiographic feature T0		
Osteophyte area (sum)	3.89 (0.52, 7.26)	0.02
Bone density (difference)	–1.08 (–2.09, –0.06)	0.04
Demographic		
BMI T0	0.92 (0.32, 1.53)	0.003
Radiographic feature T2y		
Osteophyte area (difference)	–8.26 (–15.53, –1.00)	0.03
Demographic		
BMI T2y	1.33 (0.85, 1.80)	< 0.0001
ESR T0	0.40 (0.12, 0.68)	0.01
Radiographic feature T5y		
Minimum JSW (sum)	–1.45 (–2.39, –0.51)	0.003
Osteophyte area (sum)	2.76 (0.06, 5.46)	0.05
Demographic		
BMI T5y	0.85 (0.43, 1.27)	< 0.0001
ESR T0	0.38 (0.08, 0.69)	0.01

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index for pain; ß: regression coefficient; JSW: joint space width; BMI: body mass index; ESR: erythrocyte sedimentation rate.

types might need specific treatment, which is important in clinical trial design. It is hypothesized that the specific radiographic features as defined and described in this study represent different characteristics of radiographic joint damage, and thus these features might aid in the definition of such phenotypes.

By use of KIDA measurements, the following specific and different radiographic features of knee OA could be identified: minimum, medial and lateral JSW, varus angle, osteophyte area, eminence height, and bone density. All features progressed over time, some mainly in an early phase and some later. Relationships between radiographic features and clinical outcome varied over time, possibly explained by different processes involved during different phases of the disease. The identification of these features, their mutual relation, and the relationship with clinical outcome adds to our insight on progression of different characteristics of OA early in the disease.

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