Osteoarthritis and Cartilage (2008) **16,** 234–243

doi:10.1016/j.joca.2007.06.009

Osteoarthritis and Cartilage
ICRS International Cartilage Repair Society
OARSI OSTEOARTHRITIS RESEARCH SOCIETY INTERNATIONAL

Knee Images Digital Analysis (KIDA): a novel method to quantify individual radiographic features of knee osteoarthritis in detail

A. C. A. Marijnissen Ph.D.†*, K. L. Vincken Ph.D.‡, P. A. J. M. Vos M.D.†, D. B. F. Saris M.D., Ph.D.§, M. A. Viergever Ph.D., Professor‡, J. W. J. Bijlsma M.D., Ph.D., Professor†, L. W. Bartels Ph.D.‡ and F. P. J. G. Lafeber Ph.D., Associate Professor†
† *Rheumatology and Clinical Immunology, UMC Utrecht, The Netherlands*
‡ *Image Sciences Institute, UMC Utrecht, The Netherlands*
§ *Orthopaedics, UMC Utrecht, The Netherlands*

Summary

Objective: Radiography is still the golden standard for imaging features of osteoarthritis (OA), such as joint space narrowing, subchondral sclerosis, and osteophyte formation. Objective assessment, however, remains difficult. The goal of the present study was to evaluate a novel digital method to analyse standard knee radiographs.

Methods: Standardized radiographs of 20 healthy and 55 OA knees were taken in general practise according to the semi-flexed method by Buckland-Wright. Joint Space Width (JSW), osteophyte area, subchondral bone density, joint angle, and tibial eminence height were measured as continuous variables using newly developed Knee Images Digital Analysis (KIDA) software on a standard PC.
Two observers evaluated the radiographs twice, each on two different occasions. The observers were blinded to the source of the radiographs and to their previous measurements. Statistical analysis to compare measurements within and between observers was performed according to Bland and Altman. Correlations between KIDA data and Kellgren & Lawrence (K&L) grade were calculated and data of healthy knees were compared to those of OA knees.

Results: Intra- and inter-observer variations for measurement of JSW, subchondral bone density, osteophytes, tibial eminence, and joint angle were small. Significant correlations were found between KIDA parameters and K&L grade. Furthermore, significant differences were found between healthy and OA knees.

Conclusion: In addition to JSW measurement, objective evaluation of osteophyte formation and subchondral bone density is possible on standard radiographs. The measured differences between OA and healthy individuals suggest that KIDA allows detection of changes in time, although sensitivity to change has to be demonstrated in long-term follow-up studies.

Key words: Osteoarthritis, Radiography, Digital image analysis.

Introduction

Osteoarthritis (OA) is a slowly developing degenerative joint disease, characterised by pain and functional disability. Structural changes, such as damage of the articular cartilage, changes in the subchondral bone, and secondary inflammation, are expected to originate at least in part these clinical symptoms. Despite all efforts in research on OA over the past years, a clear definition of the disorder and proper diagnostic criteria remain difficult to identify[1,2]. One of the main reasons for this difficulty is the (apparent) inconsistency between radiographic OA and symptomatic OA[3–6]. There is hardly a correlation between radiographic scores (representing structural changes) and clinical symptoms. In fact in clinical practise radiographs are primarily used to exclude other underlying reasons of pain and functional disability. Even in the case of surgical intervention, clinical symptoms, more than radiographs, are directive in decision-making. Indeed, the way radiographic images are presently read and scored makes it difficult to detect subtle changes in a short time span. It is generally appreciated that significant changes in radiographic scores take at least 1 year or even 2 years[7,8].

Both the limited association of the presently available radiographic scores with clinical symptoms and the limited discriminating abilities in case of disease progression or changes in progression due to treatment, tempted many to study novel imaging techniques, the most obvious being Magnetic Resonance Imaging (MRI). However, radiography continues to be the golden standard in imaging of OA joints since the technique is cheap, fast, and available in all hospitals. The Food and Drug Administration (FDA) (guidance for industry at www.fda.gov/cder/guidance) still demands radiographic changes to prove disease-modifying efficacy of treatment strategies. Moreover, the Group for the Respect of Ethics and Excellence in Science (GREES) recommended joint space narrowing on radiographs, in addition to pain and function as a co-primary endpoint to determine the efficacy of disease-modifying drugs[9].

Reliable objective quantitative analysis of radiographs is difficult. Except for Joint Space Width (JSW) narrowing[10,11],

*Address correspondence and reprint requests to: Mrs A.C.A. Marijnissen, Ph.D., UMC Utrecht, Rheumatology and Clinical Immunology, F02.127, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands. Tel: 31-30-2509758; Fax: 31-30-2523741; E-mail: a.c.a.marijnissen@umcutrecht.nl
Received 3 November 2006; revision accepted 13 June 2007.

parameters such as subchondral sclerosis and osteophyte formation are mostly integrated in overall grading systems that comprise multiple OA related changes on radiographs[12–14], e.g., the most frequently used composite score of Kellgren & Lawrence (K&L). This makes such grading systems less sensitive to small changes in individual parameters. Although also grading systems for individual features are used[15], both types of grading systems use very rough stepwise scoring (ordinal variables) instead of gradual detailed changes (continuous variables). This all will add to the limited correlation between radiographic changes and clinical symptoms and to the limited sensitivity to change.

To improve the sensitivity to change in the evaluation of radiographs, quantification of individual features of OA in continuous variables is required. Up to now, only JSW can be given as a continuous variable. On weight bearing radiographs, the distance between the bone ends (i.e., JSW) corresponds (at least to a certain extent) with thickness of the articular cartilage. Objective measurement of the radiographic JSW has been reported for the hip[11,16], the ankle[17,18], and the knee[19,20]. Recently, quantitative measurements of joint space narrowing have been described to be more sensitive to change than semi-quantitative ratings[21]. The accuracy of measurements of JSW can be improved by digital image analysis of the radiographs, by standardisation of radiography of the joint, and by correction for radiographic magnification[22].

At present, objective quantitative evaluation of radiographs is mainly limited to measurement of minimal and mean JSW. Objective measurement of radiographic subchondral sclerosis, osteophytes, tibial eminence, and the angle of the knee joint have not yet been developed.

Therefore, we have developed and evaluated a novel method to quantify in detail a broad spectrum of individual radiographic features of knee OA: Knee Images Digital Analysis (KIDA).

Patients and methods

RADIOGRAPHY

Semi-flexed (metatarsophalangeal [MTP]) Posterior Anterior (PA) radiographs of the tibia-femoral joint were taken under full weight bearing according to the protocol of Buckland-Wright[10,23]. The standard settings were 55 kV, 5 mA s, and focal film distance was 1.0 m with the knee against the detector. Radiographs were taken with an aluminium step wedge on the lateral side of the knee, against the detector (film) within the field of exposure, in order to quantify bone density changes in time and correct for possible magnification of the radiograph. As in routine clinical practise, different technicians took the radiographs. The images of 20 healthy knees (four males/16 females; age 30.8 ± 1.5 years, range 22–43 years) and of 55 knees with OA features (OA according to the American College of Rheumatology (ACR) criteria[24]; 31 males/24 females; age 54.5 ± 1.5 years, range 30–82 years) in different stages of the disease were used for the evaluation of OA related features using KIDA. This implicates that the study does not validate standardisation of radiographic procedures (as has been done before[10,23]) but only the digital analyses.

KIDA

KIDA is a software application for interactive analysis of radiographs of the knee, based on ImageXplorer, developed at the Image Sciences Institute, Utrecht, The Netherlands. Only radiographs that have been taken according to the defined procedures can be analysed. To facilitate standard evaluation, images are presented on the screen with the fibula located on the left side of the image. Enlargements and contrast adaptations on screen can be performed, whenever required; they do not influence the final outcome. Six consecutive steps are performed as follows.

1. Identification of the step wedge reference: The aluminium step wedge reference (15 cm × 3 cm; thickness varies from 1.2 cm to 4 cm in 15 steps) is included in the protocol (see Fig. 1) in order to be able to derive a measure for bone density and correct for magnification of the radiograph. The observer interactively indicates the four corners of the wedge, which result in the outline of the wedge, automatically drawn by the programme. The application calculates the size of the image pixels using the indicated length of the step wedge (compared to the known length of 15 cm). Additionally, based on the indicated outline of the wedge the computer identifies, with safe margins, the different steps of the wedge (see Fig. 1). The programme calculates the maximum grey value in the region of correct exposure in the characteristic curve of the X-ray film or detector. In case pixels have a value above the maximum reliable value they are given this maximum value for further calculations. To show the observer whether the maximum value is reached these pixels are coloured green on the screen. In such cases there is an underestimation of the actual density.

2. Identification of the joint: A framework of four lines (L1, L2, L3, and L4), which can separately be repositioned by the observer, is initially placed by the programme (see Fig. 1). L1 is a line touching the lateral bone edges of femur and tibia excluding osteophytes (lateral side of the joint), L2 is a line touching the two points of the greatest curvature of the femoral condyles, L3 is a line touching the two lowest points within the floor of the tibial plateau, and L4 is a line touching the medial bone edges of femur and tibia excluding osteophytes (medial side of the joint). When both the anterior margin and the posterior margin of the tibial plateau are visible, the anterior margin is used.

3. Defining the bone cartilage interface and subchondral area: Subsequently, the programme calculates the position of four perpendiculars upwards on line L2 in the lateral compartment and four in the medial compartment, with the same procedure downwards on line L3. The four perpendiculars are placed at a mutual distance 1/20 of A–B and C–D, respectively. The outer perpendiculars are placed at 2/15 A–B from A and B (lateral and medial compartments, respectively), and 2/15 C–D from C and D for the tibia (white lines in Fig. 1). Points A to D are the intersections of L2 and L3 with lines L1 and L4 (see Fig. 1). Simultaneously, circles (with a diameter of 1/20 A–B or C–D) are automatically placed with its centres on the perpendiculars. The location of the perpendiculars and the size of the circles were chosen to cover the major part of the area of interest.

The operator then interactively indicates the intersection of the perpendiculars with the edges of the femur (the cartilage bone interface) by positioning the bottom (for femur) or top (for tibia) of the 16 circles manually at the bone cartilage interface (see Fig. 1).

The programme calculates the distance between each pair of circles as a measure of JSW (four locations in the lateral compartment and four in the medial compartment). In addition, the programme calculates the mean intensity of the radiograph in each circle. Comparison of the intensity in the circles with the intensity of the step wedge reference (with known thicknesses; by local interpolation analysis)

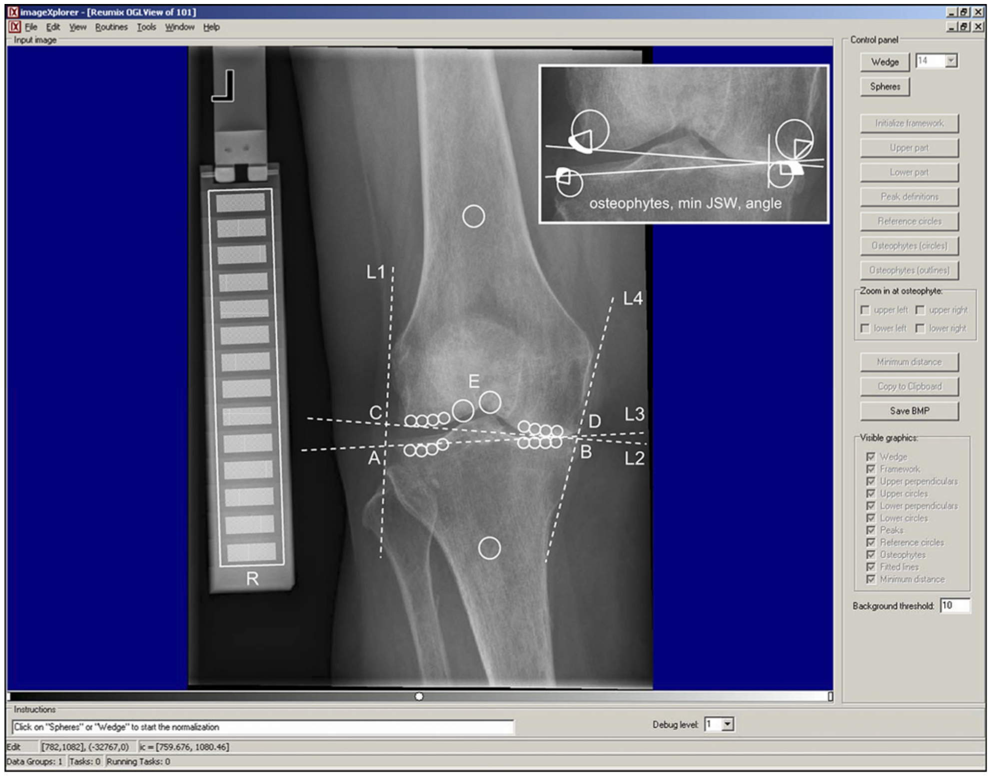

Fig. 1. Presentation of KIDA. Lines and circles are interactively indicated as described in Patients and methods. KIDA provides data on JSW, subchondral bone density, osteophyte area, the height of the tibial eminence, and the angle of the joint. The inset shows the analysis of osteophytes, minimum JSW, and the angle of the joint.

gives a measure of bone density in mm aluminium equivalent (mm Alu Eq.).

4. Defining the top of the tibial eminence: The programme places two circles, which need separately to be repositioned by the observer to indicate the top of the tibial eminence. The observer positions the bottom of the circle at the top of the tibial eminence. The programme calculates the distance from the bottom of both circles to line L3 as a measure for the height of the tibial eminence.

5. Defining the osteophyte margins: Four circles at each of the compartments of the joint (diameter = 3/20 CD and 1/10 CD for femur and tibia, respectively) are placed by the programme (Fig. 1). The size of these circles is based on the average natural curve of the bone edges of the human tibia and femur. The observer needs to reposition these circles to place them exactly into each corner of the bones forming the joint, following the original lines of the bone. Subsequently, the observer indicates the border of the osteophyte by clicking at multiple points on the outer osteophyte margin. Only the osteophyte margin within a quadrant is indicated. Although this leads to an underestimaton of the actual area, it adds to the reproducibility of the procedure. The programme calculates for each of the four compartments, the osteophyte area that is defined by the manually indicated osteophyte outer margin and the boundary of the circle positioned by the observer.

6. Joint angle and minimum JSW: From the intersection points that determine the bone cartilage interface (see under step 3), the two central circles of the four circles in the medial and lateral compartments each are used for regression analysis. This is performed for the femur and tibia providing two lines (see inset of Fig. 1) that define the joint angle as calculated by the programme. This procedure is more accurate than taking the angle between L2 and L3 because it uses for each line four instead of two points. A negative angle indicates joint space narrowing on the medial side of the joint.

Subsequently, the programme gives within the joint edges a vertical line at the narrowest point between these regression lines, suggesting the minimum JSW. Because of the curved and not fully congruent bone margins, the observer may need in a second step to reposition the two horizontal lines (this does not influence the calculation of the angle) and the vertical line in order to indicate the actual minimum joint space. The programme calculates the distance between the intersection points with the horizontal lines as a measure of minimum JSW.

Extraction of the quantitative results

The entire interactive procedure takes less than 10 min per radiograph and provides the following data. As measures for JSW, the distance between each pair of circles on femur and tibia (four values for the lateral side and four values for the medial side), the mean distance for each compartment (lateral and medial) of the joint, and the mean distance for the whole joint are given in mm. As measures for subchondral bone density the mean density of each of the 16 subchondral bone circles, the mean of the four circles for each of the four compartments (lateral femur, medial femur, lateral tibia, and medial tibia), and the mean value of all circles are given in mm Alu Eqs. The height of the tibial eminences is given in mm. The osteophyte area of each of the four outer osteophyte regions is given in mm^2. The angle of the joint is given in degrees and the minimum JSW is given in mm.

METHODS OF EVALUATION

Two observers evaluated the radiographs using KIDA, each on two different occasions with an interval of at least 1 week: one biomedical scientist (AM) and one fully unrelated non-academic. The observers were blinded to the source of the radiographs and to their previous measurements. Statistical analysis to compare measurements within and between observers was performed according to Bland and Altman[25]. In brief, the intra-observer variation in the digital analysis (KIDA) was determined by plotting the difference in the first and the second score against the mean of these two observations. Inter-observer variation in the digital analysis (KIDA) was determined by plotting the difference in the second score from one observer and the second score from the other observer against the mean of the two scores. The distance between the mean of measurement differences (the solid line in the Bland and Altman plots) and zero indicates the bias. For intra- and inter-observer variations 95% confidence intervals (C.Is.) of the differences were calculated. Assuming no systematic bias (mean of differences equals 0), 1.96 times the standard deviation (SD) defines the smallest detectable difference (SDD). This evaluation of observer reproducibility is distinctly different from a test−retest reproducibility where in addition to observer reproducibility the process of taking the images is integrated in the evaluation. To compare KIDA parameters with the most frequently used grading system for OA, radiographs were also scored using the K&L grade (PV). Individual KIDA data were compared to the overall K&L grade. Additionally, KIDA data of healthy knees were compared to those of OA knees.

STATISTICAL ANALYSIS

The Mann−Whitney *U* test was used to analyse differences between the values measured between healthy and OA knees. Spearman correlation coefficients of the individual KIDA data and the K&L grade data were calculated. $P < 0.05$ was considered to be statistically significant.

Results

KIDA can be learned in less than an hour to a non-academic. The duration of a full evaluation including data storage is between 5 min and 10 min per radiograph.

INTRA- AND INTER-OBSERVER VARIATIONS IN MEASUREMENT OF KIDA PARAMETERS

Table I depicts for each parameter mean actual values ± SD for all radiographs and intra-observer (A1−A2) and inter-observer (A2−B2) variations in the measurements. With respect to the latter, the mean difference between the first and the second score (Mean Δ), SD, range, and 95% C.I. of differences are given.

As an example, Fig. 2(A) and (B) shows the differences between two measurements of observer A (A1−A2) plotted against the mean of these measurements in the evaluation of minimum JSW (A) and subchondral bone density of the medial femur (B). Similarly, Fig. 2(C) and (D) shows the inter-observer variation of the same parameters by plotting the differences between the second measurements of observers A and B (A2−B2) against the mean of these measurements. The solid horizontal line depicts the mean of the differences, while the dashed horizontal lines depict the mean ± 1.96 times the SD of the differences.

In almost all cases, the inter-observer variation was larger than the intra-observer variation (see the 95% C.I. in Table I), although no huge differences were observed. The differences in measurement of all parameters did not relate to the actual value of the parameter: a large and a small JSW both showed similar differences in measurements between two observations (see representatives in Fig. 2).

JSW

For observer A, there were small differences between the first and the second measurements for mean, lateral, medial, and minimum JSW (see Table I; compare 'Mean Δ' with its 'SD' with the actual mean values ± SD). As an example, the intra-observer variation in measurement of minimum JSW is given in Fig. 2(A). Intra- and inter-observer variations (see Table I) in measurement of medial and minimum JSW were slightly smaller than those in measurement of mean and lateral JSW. No systematic bias was found in the JSW measurements (small distance between 'Mean Δ' and zero). Assuming one observer (A), the SDD (1.96 times the SD) for mean, lateral, medial, and minimum JSW was 0.86 mm, 1.53 mm, 0.67 mm, and 0.49 mm, respectively, in a range from 0 mm (no JSW left) to 9.7 mm (the maximum JSW measured).

SUBCHONDRAL BONE DENSITY

For observer A, there were small differences between the first and the second subchondral bone density measurements of lateral tibia, medial tibia, lateral femur, and medial femur (see Table I; compare 'Mean Δ' with its 'SD' with the actual mean values ± SD). The inter-observer variation was similar to the intra-observer variation [Table I and Fig. 2(D) compared to Fig. 2(B)]. The differences in subchondral bone density measurements did not appear to be related to the actual value of the measure for subchondral bone density [Table I and Fig. 2(B) and (D)]. No systematic bias was found in the subchondral bone density measurements. Assuming one observer (A), the SDD for lateral tibia, medial tibia, lateral femur, and medial femur was 1.06 mm Alu Eq., 0.84 mm Alu Eq., 1.08 mm Alu Eq., and 0.84 mm Alu Eq., respectively, in a range from 18.2 mm Alu Eq. (the smallest measure of bone density, which was assessed at the medial femur side) to 36.0 mm Alu Eq. (the highest measure of bone density).

EMINENCE

There were also small differences between the first and the second observation of observer A in measurement of the lateral and medial eminence (see Table I). Again no systematic bias was found in the eminence measurements. The SDD for lateral and medial eminence was 2.47 mm and 1.92 mm, respectively, in a range from 4.1 mm (the minimal height, which was measured at the lateral side) to 16.2 mm (the maximum height).

OSTEOPHYTES

Differences between the first and the second observation of observer A in osteophyte measurement were relatively large, compared to the other parameters (see Table I). A small systematic bias was found in osteophyte measurement within one observer as well as between two observers (a 'Mean Δ' range up to 1.34). The SDD for lateral tibia,

Table I

Intra- and inter-observer variations according to Bland and Altman. Mean ± SD depicts the mean actual value of each parameter of all radiographs. Mean Δ = mean difference between the first and the second observation of all radiographs; SD = standard deviation of mean differences between the first and the second observations; range = range of differences between the first and the second observations; 95% C.I. = mean difference ± 1.96 times the SD

Observer	Mean ± SD	Mean Δ	SD	Range	95% C.I.
Mean JSW measurements (mm)					
A1−A2	5.1 ± 1.2	0.04	0.44	−2.58−1.06	−0.82; 0.90
A2−B2	5.1 ± 1.1	−0.05	0.52	−2.48−2.03	−1.10; 0.96
Lateral JSW measurements (mm)					
A1−A2	6.1 ± 1.5	0.03	0.78	−5.02−2.05	−1.50; 1.56
A2−B2	6.1 ± 1.5	−0.04	0.99	−5.10−4.38	−1.98; 1.90
Medial JSW measurements (mm)					
A1−A2	4.2 ± 1.6	0.06	0.34	−1.41−1.66	−0.61; 0.73
A2−B2	4.2 ± 1.6	−0.07	0.38	−1.83−0.49	−0.81; 0.67
Minimum JSW measurements (mm)					
A1−A2	2.8 ± 1.7	−0.02	0.25	−0.80−0.59	−0.51; 0.47
A2−B2	2.9 ± 1.7	−0.11	0.52	−2.45−1.12	−1.13; 0.91
Subchondral bone density lateral tibia (mm Alu Eq.)					
A1−A2	29.6 ± 4.2	−0.04	0.54	−1.66−2	−1.10; 1.02
A2−B2	29.7 ± 4.2	−0.17	0.60	−2.23−2.21	−1.35; 1.01
Subchondral bone density medial tibia (mm Alu Eq.)					
A1−A2	31.3 ± 4.6	0.06	0.43	−1.36−2	−0.78; 0.90
A2−B2	31.3 ± 4.6	−0.09	0.56	−1.39−3.29	−1.19; 1.01
Subchondral bone density lateral femur (mm Alu Eq.)					
A1−A2	28.6 ± 4.6	0.00	0.55	−1.81−2.25	−1.08; 1.08
A2−B2	28.6 ± 4.6	−0.11	0.48	−1.29−1.96	−1.05; 0.83
Subchondral bone density medial femur (mm Alu Eq.)					
A1−A2	29.8 ± 5.2	0.06	0.43	−1.75−2	−0.78; 0.90
A2−B2	29.7 ± 5.1	−0.11	0.39	−1.05−1.67	−0.87; 0.65
Tibial eminence lateral (mm)					
A1−A2	10.0 ± 2.1	−0.07	1.26	−6.04−4.38	−2.54; 2.40
A2−B2	10.0 ± 2.1	−0.03	0.90	−2.97−3.34	−1.79; 1.73
Tibial eminence medial (mm)					
A1−A2	11.6 ± 2.0	−0.08	0.98	−5.28−2.22	−2.00; 1.84
A2−B2	11.7 ± 1.8	−0.22	1.44	−10.23−3.58	−3.04; 2.60
Osteophyte lateral tibia (mm^2)					
A1−A2	6.4 ± 6.5	−1.34	4.11	−22.71−7.66	−9.40; 6.72
A2−B2	6.7 ± 7.4	0.53	3.43	−10.82−11.34	−6.19; 7.25
Osteophyte medial tibia (mm^2)					
A1−A2	9.9 ± 6.8	−0.31	2.36	−9.97−5.37	−4.94; 4.32
A2−B2	9.3 ± 6.4	1.23	2.97	−5.37−13.39	−4.59; 7.05
Osteophyte lateral femur (mm^2)					
A1−A2	5.4 ± 5.8	−0.71	3.46	−11.55−19.05	−7.49; 6.07
A2−B2	5.3 ± 6.6	0.95	5.36	−29.51−13.02	−9.56; 11.46
Osteophyte medial femur (mm^2)					
A1−A2	3.7 ± 7.3	−0.11	1.64	−4.95−4.39	−3.32; 3.10
A2−B2	3.6 ± 7.2	0.55	3.99	−20.96−9.27	−7.27; 8.37
Angle between femur and tibia (°)					
A1−A2	3.0 ± 2.0	−0.11	1.03	−5.45−2.69	−2.13; 1.92
A2−B2	3.0 ± 2.1	−0.08	1.10	−4.41−2.99	−2.24; 2.09

medial tibia, lateral femur, and medial femur was 8.1 mm^2, 4.6 mm^2, 6.8 mm^2, 3.2 mm^2, respectively, in a range from 0 mm^2 (the minimal area) to 35.0 mm^2 (the maximum area).

ANGLE BETWEEN FEMUR AND TIBIA

Differences between the first and the second observation of observer A in measurement of the angle of the joint were also small (see Table I). The SDD was 2.0° in a range from 0° to 9.1°. For these calculations, the angle was defined as an absolute value (*viz.* negative angles as a result of medial JSW narrowing were taken as a positive value). In fact, 90.7% of the angles were negative (medial JSW narrowing) and 9.3% were positive (lateral JSW narrowing). On average, the angle for medial JSW narrowing was −3.1° ± 2.1° and for lateral JSW narrowing +2.7° ± 2.4° (mean ± SD).

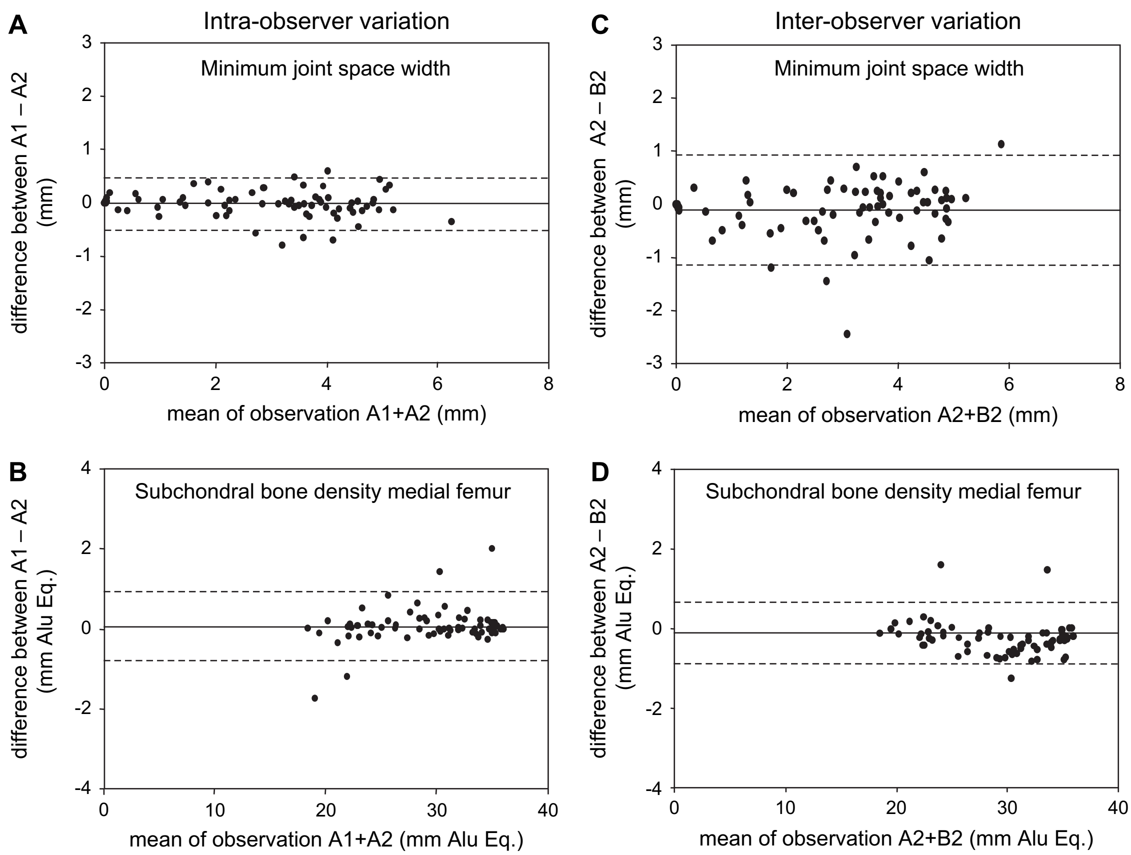

Fig. 2. Representative Bland and Altman plots for intra- and inter-observer variations of individual parameters of KIDA. The mean difference between two observations is depicted (solid horizontal lines) with 1.96 times the SD of the measured differences (dashed lines). (A) and (B) Differences between two measurements of observer A (A1–A2) are plotted against the mean of these measurements in the evaluation of minimum JSW (A) and subchondral bone density of the medial femur (B). (C) and (D) Differences between the second measurements of observers A and B (A2–B2) are plotted against the mean of these measurements.

CORRELATION BETWEEN INDIVIDUAL KIDA PARAMETERS

Most of the individual KIDA parameters correlated statistically significantly with other KIDA parameters. Strikingly, minimum JSW correlated statistically significantly with almost all other individual KIDA parameters, whereas the other JSW parameters (mean, lateral, and medial) hardly correlated statistically with the other parameters (Table II). It was also interesting to see that subchondral bone density in the tibia correlated well with the bone density in the femur and that also lateral and medial bone density correlated well despite uni-compartmental JSW narrowing in most cases.

COMPARISON WITH K&L GRADE

Individual KIDA parameters correlated statistically significantly with the overall K&L grade as is shown in Fig. 3 and Table II, except for measurement of tibial eminence and joint angle deviation. As expected, there was a good correlation between osteophyte measurement and K&L grade ($R = 0.57$). But interestingly this was also found for e.g., bone density parameters. Importantly, for each of the parameters within *one* K&L grade a large variation exists in KIDA grading. For example, within a K&L gradation of 0 a large range in minimum JSW and osteophyte measurement is present.

DIFFERENCES BETWEEN HEALTHY AND OA KNEES

Differences between healthy and OA knees can be objectively measured using KIDA. Statistical significant differences were observed for all KIDA parameters except for the lateral JSW (see Fig. 4) and the joint angle deviation ($2.6° \pm 0.4°$ vs $3.2° \pm 0.3°$ for healthy and OA knees, respectively). K&L grade differed also statistically significantly between healthy and OA knees ($K\&L = 0.3 \pm 0.1$ and 1.3 ± 0.1, respectively).

Discussion

In this study we have described a novel digital method for the evaluation of radiographs of OA knees: KIDA. We have compared KIDA to the frequently used K&L grading system. In addition, we used the new method to evaluate differences in KIDA parameters in healthy and OA knees. The study did not evaluate radiographic procedures (test–retest reproducibility) but focussed on the reproducibility of KIDA. This limits the conclusions that can be drawn in regard to calculations for the number of patients to be included for clinical trials because variation in the radiographic procedures (even though we used a validated standard[10,23]) is expectedly greater than that in the KIDA measurement. Test–retest evaluations will be performed in the near future.

Table II

Correlations between individual KIDA parameters and K&L grade. Spearman correlation coefficients are given. Asterisks indicate statistical significant correlation coefficients, while the non-significant values are given in italics. High significant correlation coefficients (≥0.5) are given in bold font

			Subchondral bone density				Osteophyte				JSW				Tibial eminence		Angle	K&L
			Lateral femur	Medial femur	Lateral tibia	Medial tibia	Lateral femur	Medial femur	Lateral tibia	Medial tibia	Lateral	Medial	Mean	Min.	Lateral	Medial		
Subchondral bone density	Femur	Lateral		0.69*	0.94*	0.72*	0.37*	0.22	0.30*	0.42*	0.14	0.02	0.05	−0.34*	0.53*	0.42*	0.05	0.16
		Medial	0.69*		0.65*	0.93*	0.31*	0.43*	0.19	0.41*	0.11	−0.39*	−0.19	−0.55*	0.22	0.05	0.18	0.27*
	Tibia	Lateral	0.94*	0.65*		0.73*	0.33*	0.23*	0.32*	0.31*	0.23	0.13	0.19	−0.21	0.51*	0.37*	−0.02	0.10
		Medial	0.72*	0.93*	0.73*		0.31*	0.44*	0.17	0.36*	0.19	−0.34*	−0.10	−0.48*	0.26*	0.08	0.15	0.22
Osteophyte	Femur	Lateral	0.37*	0.31*	0.33*	0.31*		0.12	0.40*	0.38*	−0.10	−0.10	−0.21	−0.35*	0.31*	0.26*	0.16	0.42*
		Medial	0.22	0.43*	0.23*	0.44*	0.12		0.28*	0.32*	0.17	−0.20	−0.12	−0.43*	−0.09	0.12	0.24*	0.45*
	Tibia	Lateral	0.30*	0.19	0.32*	0.17	0.40*	0.28*		0.45*	0.07	0.12	0.03	−0.28*	0.26*	0.39*	0.14	0.53*
		Medial	0.42*	0.41*	0.31*	0.36*	0.38*	0.32*	0.45*		0.01	−0.14	−0.17	−0.50*	0.30*	0.37*	0.17	0.57*
JSW		Lateral	0.14	0.11	0.23	0.19	−0.10	0.17	0.07	0.01		0.14	0.73*	0.29*	0.23*	0.27*	0.33*	−0.15
		Medial	0.02	−0.39*	0.13	−0.34*	−0.10	−0.20	0.12	−0.14	0.14		0.71*	0.67*	0.24*	0.44*	−0.52*	−0.26*
		Mean	0.05	−0.19	0.19	−0.10	−0.21	−0.12	0.03	−0.17	0.73*	0.71*		0.71*	0.30*	0.38*	−0.24*	−0.39*
		Minimum	−0.34*	−0.55*	−0.21	−0.48*	−0.35*	−0.43*	−0.28*	−0.50*	0.29*	0.67*	0.71*		−0.04	0.07	−0.48*	−0.57*
Tibial eminence		Lateral	0.53*	0.22	0.51*	0.26*	0.31*	−0.09	0.26*	0.30*	0.23*	0.24*	0.30*	−0.04		0.48*	−0.03	−0.15
		Medial	0.42*	0.05	0.37*	0.08	0.26*	0.12	0.39*	0.37*	0.27*	0.44*	0.38*	0.07	0.48*		−0.04	0.14
Angle			0.05	0.18	−0.02	0.15	0.16	0.24*	0.14	0.17	0.33*	−0.52*	−0.24*	−0.48*	−0.03	−0.04		0.30*
K&L grade			0.16	0.27*	0.10	0.22	0.42*	0.45	0.53*	0.57*	−0.15	−0.26*	−0.39*	−0.57*	−0.15	0.14	0.30*	

The results demonstrate KIDA to be a reliable method to quantify and document (for follow-up) the individual radiographic parameters of knee OA. The small inter-observer variations in KIDA measurements indicate that similar results will be obtained when different observers evaluate knee radiographs. To our knowledge, KIDA is the first method that provides quantification of subchondral bone density, osteophyte area, and the height of the tibial eminence in addition to JSW measurement and measurement of the joint angle on standard knee radiographs (all as a continuous variable). The statistical significant differences between healthy and OA knees demonstrate the usefulness of the KIDA parameters. Relative mild OA joints were included as indicated by an average K&L grade of 1.3 which is the most relevant group for the evaluation of follow-up, e.g., in case of treatment. The observed SDDs suggest sufficient distinguishing capacity for all parameters, although longitudinal follow-up has to prove this.

The large variation in individual KIDA parameters within a single K&L grade indicates the power of KIDA parameters to distinguish a gradual change in joint damage for individual parameters. This clearly makes KIDA evaluation more sensitive than grading according to K&L. Many other methods of radiography and computer evaluation are probably more sensitive than grading according to K&L, however, they have their limitations in clinical and research practise. Since our intention was to develop a solid, reliable, and simply to use the method to evaluate standard radiographs, KIDA was not compared to these evaluation methods but to the K&L grade, which is most commonly used to determine the severity of OA in clinical and research settings.

A shortcoming in quantification of subchondral bone density on radiographs in general is the scattering that occurs during the radiographic imaging process (secondary radiation in the form of Compton photons). This influences the black/white intensity of the radiograph, independently of the thickness of the bone, which precludes measurement of absolute bone density values using standard radiography[26]. However, to investigate the ability to detect changes in subchondral bone density using plain radiographs, the density of the bone on the radiograph was compared to the density of a step wedge reference on the same radiograph. A limitation in the measurement of subchondral bone density on the standard radiographs used by KIDA was found in the fact that a maximum reliable value of bone density is reached occasionally on standard radiographs. This maximum value is calculated in the (linear) region of the values found for the step wedge. Pixels in the knee with a density value above the maximum reliable value are given the maximum value for further calculations. In these cases, the actual bone density is underestimated and in that respect the sensitivity to detect changes in the higher bone density values decreased.

With respect to osteophyte measurement a small systematic bias was found for one observer as well as for two different observers, which makes the actual SDD larger in practise. Moreover, the value obtained is only a surrogate measure (two dimensional area) of the actual osteophyte (three dimensional) present. Also the degree of mineralisation of the osteophyte will influence the measurement. However, except for one method based on microfocal radiographs described in 1991 by Buckland-Wright and colleagues[27], KIDA is the only method that provides quantification of osteophytes as a continuous variable on standard radiographs and hence might be more sensitive to measure differences in time than the presently available

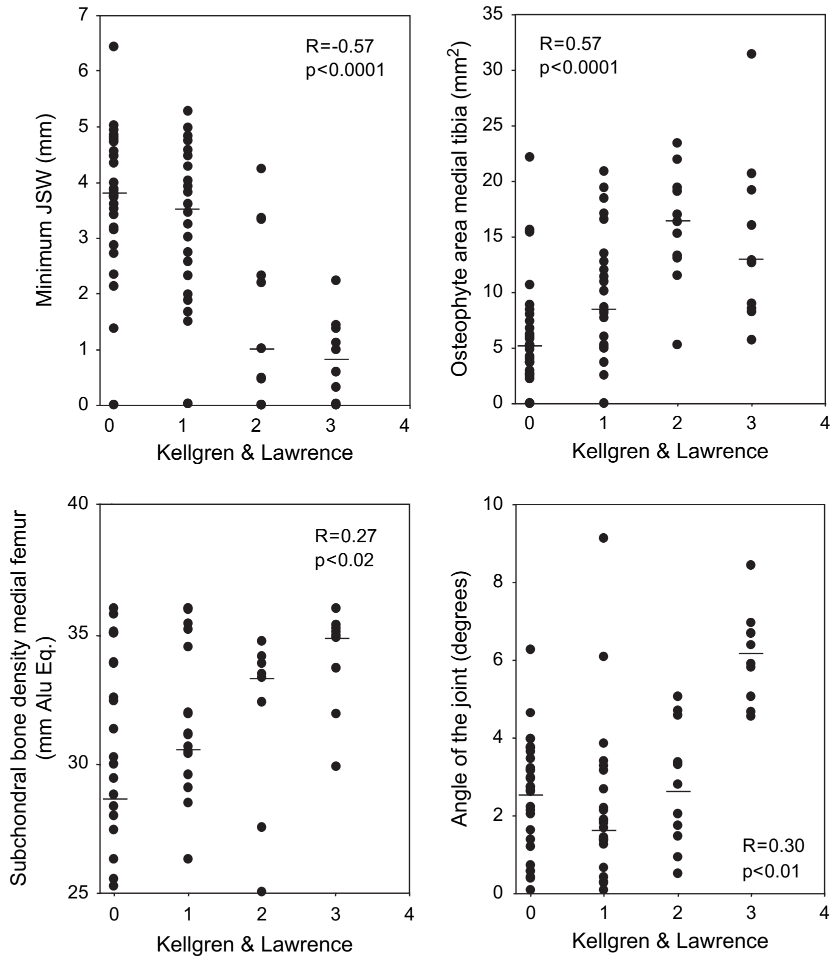

Fig. 3. Comparison of individual parameters of KIDA with the overall K&L grade for OA. Values of individual radiographs with the median values for each K&L grade (horizontal line) are depicted. $N=30$, 23, 12, and 10 for K&L grade 0, 1, 2, and 3, respectively.

grading systems. This is also indicated by the large difference in osteophyte area within one single K&L grade. Moreover, osteophyte area shows a good correlation with the K&L grade, is statistically significantly different between healthy and OA knees, and correlates with subchondral bone density parameters (and not JSW parameters), which all together indicates that osteophyte measurement using KIDA might be of value, despite a relatively large SDD.

To our knowledge, it is still unclear whether the tibial eminences undergo changes during the development of OA and whether these changes are OA specific. KIDA gives researchers a tool to evaluate potential changes in the height of the tibial eminences in the development and progression of OA.

Sensitivity to changes has not been evaluated in the present study. Minimum joint space narrowing is identified to be ~0.2 mm per year, when manually measured[28]. In this respect for an individual patient follow-up, evaluation of JSW using KIDA would need at least 2 years. However, for populations this will be much less, depending on the size of the population. This corroborates that quantitative measurements of joint space narrowing have been described to be more sensitive to change than semi-quantitative measurements[21]. Thus far, there is no qualitative information on the rate of changes in subchondral bone density, osteophytes, eminence, and joint angle deviation in the process of OA. Except for lateral JSW and joint angle deviation, all parameters were statistically significantly different between healthy and OA knees. However, follow-up studies are required to see whether KIDA is indeed sensitive enough to measure changes in OA parameters in an acceptable period of time. In addition, follow-up studies are required to demonstrate whether changes in angle deviations and subluxations during the process of OA influence the reliability of KIDA, e.g., with respect to the location of the framework.

Most of the individual KIDA parameters correlated statistically significantly with the other KIDA parameters. Strikingly, within the JSW measurements, the minimum JSW correlated statistically significantly with almost all other KIDA parameters. Therefore, the minimum JSW seems to be the most sensitive JSW parameter to evaluate in OA, as suggested before[29] and apparently represents the process of OA in general. Additionally, a significant negative correlation was found between medial JSW and subchondral bone density at the medial side of the joint for tibia and femur. Thus at a fixed location, a lower JSW is related to a higher bone density. The presently described evaluation method provides a tool to evaluate such relations in more detail in future studies involving a larger number of OA knees with a range of disease severity.

A lot of current research in OA is focussed on biochemical markers of bone and cartilage remodelling, which are

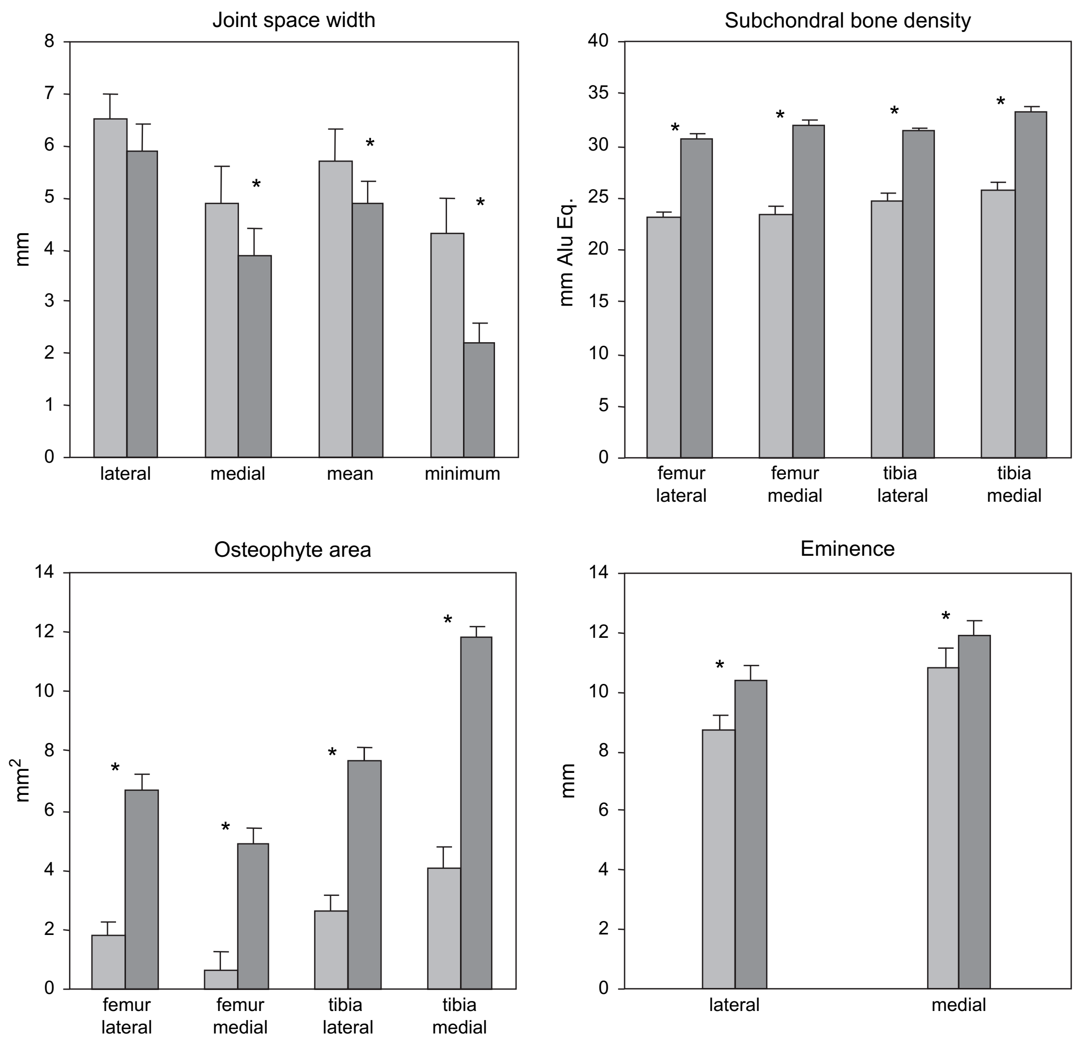

Fig. 4. Differences between healthy and OA knees. Mean ± S.E.M. is depicted for healthy knees (light grey) and OA knees (dark grey). *Statistically significant differences in individual parameters between OA and healthy knees are depicted.

being tested to predict OA and measure disease progression[30–32]. These studies are hampered by the availability of proper imaging parameters for the ‘actual’ cartilage and bone changes. KIDA may be very helpful in this respect.

Radiography is still the golden standard for imaging of OA joints and the FDA demands radiographic changes to prove disease-modifying efficacy of treatment strategies. Therefore, KIDA might be a worthy addition for the evaluation of progression of disease in knee OA cohorts and the evaluation of treatment efficacy in prospective clinical trials on knee OA.

Acknowledgements

We acknowledge Marja Lafeber for her work as observer A. This study was supported by the Dutch Arthritis Association.

References

1. McAlindon T, Dieppe P. Osteoarthritis: definitions and criteria. Ann Rheum Dis 1989;48(7):531–2.
2. Peat G, Thomas E, Duncan R, Wood L, Hay E, Croft P. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. Ann Rheum Dis 2006.
3. Dieppe PA, Cushnaghan J, Shepstone L. The Bristol ‘OA500’ study: progression of osteoarthritis (OA) over 3 years and the relationship between clinical and radiographic changes at the knee joint. Osteoarthritis Cartilage 1997;5(2):87–97.
4. Hadler NM. Knee pain is the malady—not osteoarthritis. Ann Intern Med 1992;116(7):598–9.
5. Hochberg MC, Lawrence RC, Everett DF, Cornoni-Huntley J. Epidemiologic associations of pain in osteoarthritis of the knee: data from the National Health and Nutrition Examination Survey and the National Health and Nutrition Examination-I Epidemiologic Follow-up Survey. Semin Arthritis Rheum 1989;18(4 Suppl 2):4–9.
6. Lethbridge-Cejku M, Scott WW Jr, Reichle R, Ettinger WH, Zonderman A, Costa P, *et al.* Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore longitudinal study of aging. Arthritis Care Res 1995;8(3):182–8.

7. Boegard TL, Rudling O, Petersson IF, Jonsson K. Joint space width of the tibiofemoral and of the patellofemoral joint in chronic knee pain with or without radiographic osteoarthritis: a 2-year follow-up. Osteoarthritis Cartilage 2003;11(5):370–6.
8. Vignon E, Conrozier T, Hellio Le Graverand MP. Advances in radiographic imaging of progression of hip and knee osteoarthritis. J Rheumatol 2005;32(6):1143–5.
9. Abadie E, Ethgen D, Avouac B, Bouvenot G, Branco J, Bruyere O, *et al*. Recommendations for the use of new methods to assess the efficacy of disease-modifying drugs in the treatment of osteoarthritis. Osteoarthritis Cartilage 2004;12(4):263–8.
10. Buckland-Wright JC, Ward RJ, Peterfy C, Mojcik CF, Leff RL. Reproducibility of the semiflexed (metatarsophalangeal) radiographic knee position and automated measurements of medial tibiofemoral joint space width in a multicenter clinical trial of knee osteoarthritis. J Rheumatol 2004;31(8):1588–97.
11. Conrozier T, Lequesne M, Favret H, Taccoen A, Mazieres B, Dougados M, *et al*. Measurement of the radiological hip joint space width. An evaluation of various methods of measurement. Osteoarthritis Cartilage 2001;9(3):281–6.
12. Ahlback S. Osteoarthrosis of the knee. A radiographic investigation. Acta Radiol Diagn (Stockh) 1968;(Suppl 72)
13. Croft P. An introduction to the Atlas of standard radiographs of arthritis. Rheumatology (Oxford) 2005;44(Suppl 4):iv42.
14. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16(4):494–502.
15. Altman RD, Hochberg M, Murphy WA Jr, Wolfe F, Lequesne M. Atlas of individual radiographic features in osteoarthritis. Osteoarthritis Cartilage 1995;(3 Suppl A):3–70.
16. 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):988–94.
17. Lofvenberg R, Karrholm J, Lund B. The outcome of nonoperated patients with chronic lateral instability of the ankle: a 20-year follow-up study. Foot Ankle Int 1994;15(4):165–9.
18. Marijnissen AC, Vincken KL, Viergever MA, van Roy HL, Van Roermund PM, Lafeber FP, *et al*. Ankle images digital analysis (AIDA): digital measurement of joint space width and subchondral sclerosis on standard radiographs. Osteoarthritis Cartilage 2001;9(3):264–72.
19. Buckland-Wright JC, Bird CF, Ritter-Hrncirik CA, Cline GA, Tonkin C, Hangartner TN, *et al*. X-ray technologists' reproducibility from automated measurements of the medial tibiofemoral joint space width in knee osteoarthritis for a multicenter, multinational clinical trial. J Rheumatol 2003;30(2):329–38.
20. Conrozier T, Favret H, Mathieu P, Piperno M, Provvedini D, Taccoen A, *et al*. Influence of the quality of tibial plateau alignment on the reproducibility of computer joint space measurement from Lyon schuss radiographic views of the knee in patients with knee osteoarthritis. Osteoarthritis Cartilage 2004;12(10):765–70.
21. Mazzuca SA, Brandt KD, Katz BP, Lane KA, Buckwalter KA. Comparison of quantitative and semiquantitative indicators of joint space narrowing in subjects with knee osteoarthritis. Ann Rheum Dis 2006;65(1):64–8.
22. Buckland-Wright C. Current status of imaging procedures in the diagnosis, prognosis and monitoring of osteoarthritis. Baillieres Clin Rheumatol 1997;11(4):727–48.
23. Buckland-Wright JC, Wolfe F, Ward RJ, Flowers N, Hayne C. Substantial superiority of semiflexed (MTP) views in knee osteoarthritis: a comparative radiographic study, without fluoroscopy, of standing extended, semiflexed (MTP), and schuss views. J Rheumatol 1999;26(12):2664–74.
24. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, *et al*. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8):1039–49.
25. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986;1(8476):307–10.
26. Webber CE. Photon absorptiometry, bone densitometry and the challenge of osteoporosis. Phys Med Biol 2006;51(13):R169–85.
27. Buckland-Wright C, Macfarlane DG, Jasani MK, Lynch JA. Quantitative microfocal radiographic assessment of osteoarthritis of the knee from weight bearing tunnel and semi-flexed standing views. J Rheumatol 1994;21:1734–41.
28. Brandt KD, Mazzuca SA, Katz BP, Lane KA, Buckwalter KA, Yocum DE, *et al*. Effects of doxycycline on progression of osteoarthritis: results of a randomized, placebo-controlled, double-blind trial. Arthritis Rheum 2005;52(7):2015–25.
29. Vignon E, Conrozier T, Piperno M, Richard S, Carrillon Y, Fantino O. Radiographic assessment of hip and knee osteoarthritis. Recommendations: recommended guidelines. Osteoarthritis Cartilage 1999;7(4):434–6.
30. Degroot J, Bank RA, Tchetverikov I, Verzijl N, TeKoppele JM. Molecular markers for osteoarthritis: the road ahead. Curr Opin Rheumatol 2002;14(5):585–9.
31. Garnero P. Use of biochemical markers to study and follow patients with osteoarthritis. Curr Rheumatol Rep 2006;8(1):37–44.
32. Poole AR. Can serum biomarker assays measure the progression of cartilage degeneration in osteoarthritis? Arthritis Rheum 2002;46(10):2549–52.