Objective assessments of medial osteoarthritic knee severity by MRI: new computer software to evaluate femoral condyle contours

Nobuyasu Ochiai · Takahisa Sasho · Masamichi Tahara · Atsuya Watanabe ·
Kei Matsuki · Satoshi Yamaguchi · Yoichi Miyake · Toshiya Nakaguchi ·
Yuichi Wada · Hideshige Moriya

Received: 7 July 2009 / Revised: 30 July 2009 / Accepted: 18 August 2009 / Published online: 8 September 2009
© Springer-Verlag 2009

Abstract An irregular contour of the medial femoral condyle (MFC) on magnetic resonance imaging (MRI) appears to indicate the severity of medial-type knee osteoarthritis (OA). The purpose of this study was to establish a system to enable objective assessments of OA knee severity using newly developed software that semi-automatically measures irregularity of the MFC. (1) We evaluated 48 patients aged 50–83 years with 55 knees of medial-type OA. The following scores were recorded: Lysholm score, visual analogue scale (VAS) and the Japanese Knee Osteoarthritis Measure (JKOM). MFC irregularity was automatically calculated by newly programmed computer software. Four parameters for condyle irregularity were calculated: (a) the average thickness of the contour (ATC), (b) the ratio of the upper surface length to the lower surface length of the contour (RUL), (c) average squared thickness of the contour

(ASTC) and (d) standard deviation of the contour thickness (SDC). (2) Nine knees that underwent total knee arthroplasty were further analysed histopathologically and compared with irregularity score. Statistically, the RUL and SDC were significantly correlated with the Lysholm score, VAS and JKOM, with good reliability. Histological examinations showed that an irregular contour reflected the density of cystic lesions formed in subchondral bone. An irregularity of MFC on MRI is correlated with OA disease severity clinically and histopathologically. The new computer software is useful to objectively assess OA disease severity.

Introduction

Osteoarthritis (OA) of the knee joint is a common joint pathology. X-ray examination is generally performed to assess the status of the OA knee joint, as it identifies the characteristic features of osteophytes, thickening of subchondral bone, cyst formation, malalignment and reduction of joint space due to cartilage loss. Among the indices to assess severity of OA using X-ray, the Kellgren-Lawrence (K/L) scale [1, 2] is frequently used and believed to be mostly reliable. However, its actual relationship with clinical severity of OA is controversial.

Magnetic resonance imaging (MRI) has also been used to evaluate OA knee joints due to its ability to detect cartilage abnormalities, osteophytes, subarticular cysts, bone attrition, synovitis, meniscal degeneration, bone marrow oedema, joint effusion, intra-articular loose body and periarticular cysts [3]. However, the clinical meanings of these abnormalities are not fully defined. One reason for this might be that the chief complaint of most patients is not

Nobuyasu Ochiai and Takahisa Sasho contributed equally to this study.

N. Ochiai · T. Sasho (✉) · M. Tahara · K. Matsuki ·
S. Yamaguchi · H. Moriya
Department of Orthopedic Surgery, Graduate School of Medicine,
Chiba University,
1-8-1 Inohana, Chuo-ku,
Chiba 260-8670, Japan
e-mail: sasho@faculty.chiba-u.jp

A. Watanabe · Y. Wada
Department of Orthopaedic Surgery,
Teikyo University Ichihara Hospital,
Chiba, Japan

Y. Miyake · T. Nakaguchi
Research Center for Frontier Medical engineering,
Chiba University,
Chiba, Japan

deformity but knee pain, and the pain mechanisms of OA are not fully understood.

Recent evidence suggests that the subchondral bone is important for both pain origination and OA progression [4–6]. On MRI, contours of the femoral condyle or the tibial plateau are often depicted with irregularities, which could correspond to thickening of subchondral bone seen on X-ray [7]. In a pilot study, we reported that irregularities of the femoral condyle on MRI and knee functional scores were inter-related. In that study, calculation of irregularity was done with software that was developed for another purpose [8]. This result prompted us to develop new computer software that exclusively measures the irregularity of the femoral condyle.

Our hypothesis is that an irregular contour of the femoral condyle on MRI could be an indicator of OA disease severity and that measuring the irregularity of the contour should enable us to objectively assess OA severity. The purpose of this study was to develop new computer software that could exclusively measure the irregular contour of the femoral condyle and establish a reliable index that reflected OA severity. The relationship between OA clinical severity and femoral condyle irregularity was examined. Histological examination was performed as well.

Materials and methods

Patients and clinical assessments

Forty-eight consecutive patients with a total of 55 knee joints were recruited for this study. Patients with a history of trauma, previous surgery or inflammatory arthritis were excluded. Patients' mean age was 72.8 (range 50–83) years. None had prior surgical treatment. Informed consent was obtained from all patients after the nature of the examinations had been fully explained. All examinations were performed in accordance with the rules and regulations of the local human research committee. All patients were clinically examined at their first visit. They were scored using the Lysholm score [9], visual analogue scale [(VAS) on a 100-cm scale: 0 = no pain; 100 = most severe pain] and the Japanese Knee Osteoarthritis Measure (JKOM) [10]. Lysholm scores without items for instability were used. The JKOM is a counterpart of the Western Ontario and McMaster Osteoarthritis Index (WOMAC) that was developed for assessing Japanese OA patients by taking the Japanese lifestyle into account. It has proved to be as good as or better than the WOMAC or the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) in terms of its reliability and validity [10].

Imaging

All patients underwent MRI of the affected knees within two weeks of their first visit. MRI was performed with a 1.5-T scanner (Signa, GE Medical Systems) equipped with a knee surface coil. The sequence used in this study was sagittal fast spin echo (FSE) proton density (TR 2,000 ms, TE 16 ms, field of view 14–16 cm, matrix 512×512 , number of excitations = 2, and slice thickness = 4 mm without an interslice gap). Three sagittal slices that represented the centre of the medial femoral condyle (MFC) were selected for analysis by two orthopaedic surgeons who reached a consensus without knowledge of patient age or sex. The lateral femoral condyle (LFC) was assessed as well. X-ray grading employing the K/L scale [1] on weight-bearing radiographs was also recorded.

Software interface

Irregularity of the contour of the femoral condyle was calculated by computer software that was programmed in MATLAB6.5 (Cyber Net Systems, Tokyo). Digital Imaging and Communication in Medicine (DICOM) data can be incorporated directly with this software. The procedures used to measure the irregularity of the contour of the MFC were as follows: (1) Images to be assessed were selected. Images that represented the centre of the medial compartment were selected. Usually, six or seven images were taken for a medial compartment and three slices that represented the centre of the compartment were selected. (2) The image was converted to black and white (Fig. 1b). The threshold between black and white was determined by the histogram of the dots comprising images. With the vertical axis defined as the number of dots and the horizontal axis as the luminescence of dots, the histograms of these images usually consisted of two or three peaks. The threshold was determined manually so as to leave only the first peak. This meant that only very low luminescence dots remained; i.e., only very black dots. (3) The contour of the MFC was extracted (Fig. 1c), after which the upper and the lower surfaces of the extracted contour were automatically traced (Fig. 1d). Using these two lines, four parameters reflecting irregularity were automatically calculated: (a) average thickness of the contour (ATC), (b) ratio of the length of the upper surface to the lower surface length of the contour (RUL), (c) average squared thickness of the contour (ASTC) and (d) standard deviation of contour thickness (SDC). Theoretically, the more obvious the irregularity or thickening becomes, the larger the ATC, RUL, ASTC and SDC values become.

Fig. 1 Procedures to calculate irregularity of the condyle. **a** Image to be assessed is selected on the personal computer (PC). **b** The image is then converted to black and white. **c** Only the condyle contour is extracted. **d** The upper and lower surfaces of the extracted contour are traced, making two lines. Using these two lines, parameters reflecting irregularity are calculated

Interobserver and intraobserver reliabilities

Using ten randomly selected knees of the 55 knees evaluated, intra- and interrater reliabilities, intraclass correlation coefficient (ICC) (1, 1) and ICC (2, 1) were determined.

Specimens and histological evaluation

Nine knees that underwent total knee arthroplasty (TKA) following MRI assessments were used for this study. At the time of TKA, the weight-bearing areas of the MFC and the LFC were obtained. Specimens were immediately fixed in 4% paraformaldehyde in phosphate-buffered saline for 24 h. The MFC and LFC were demineralised in 20% ethylenediaminetetraacetic acid (EDTA) at room temperature for six weeks. They were then embedded in paraffin. Sagittal sections (6 μ m) were made and mounted on glass slides. Following staining with Mayer's haematoxylin solution and 1% eosin alcohol solution (H&E staining), the total number of cystic lesions that invaded the subchondral bone plate or calcified zone were counted from three slides that corresponded to weight-bearing areas. Density of cystic lesions was expressed as the number of cystic lesions per 10-mm-length of specimen [11]. Correlation of parameters related to irregularity of the contour on MRI and the density of cystic lesions were examined.

Correlation of contour irregularity and clinical assessments

Correlations between parameters related to irregularity and the clinical score or the numbers of cystic lesions were analysed using Pearson's correlation coefficient with Statview 4.1 (Abacus, Berkeley, CA, USA). The p value was obtained from an analysis of variance, and statistical significance was defined as $p < 0.05$.

Contour irregularity and clinical assessments of each K/L group

Post hoc test (Bonferroni/Dunn) was used for comparing contour irregularity and clinical assessments among each K/L group (Statview 4.1) where $p < 0.05$ or 0.01 was considered significant.

Results

Interrater and intraobserver reliabilities

Interrater reliabilities were ATC=0.463, RUL=0.811, ASTC=0.384, and SDC=0.891. Intrarater reliabilities were ATC=0.573, RUL=0.834, ASTC=0.342, and SDC=0.923. (Measurements are defined in Materials and Methods.)

Fig. 2 Relationships between the standard deviation of the contour thickness (SDC) values and knee scores. The SDC scores are negatively correlated with **a** the Lysholm scores and **b** the Japanese Knee Osteoarthritis Measure (JKOM) scores, whereas **c** the SDC and visual analogue scale (VAS) are positively correlated

Therefore, the RUL and the SDC were selected for further analysis.

Clinical scores and X-ray grading

The average Lysholm score was 25.65 ± 11.01 (range 5–47), the average VAS was 74.03 ± 18.03 (range 30–100) and the average JKOM was 49.33 ± 18.81 (range 8–90). Thirteen, seven, 23 and 12 knees were classified as K/L I, II, III and IV, respectively.

Correlations between clinical assessments and contour irregularity

1. RUL and knee Scores

The RUL values and Lysholm scores were negatively correlated ($r = -0.448$, $p = 0.0016$), as were the RUL and the JKOM ($r = -0.623$, $p < 0.0001$). A significant positive correlation was found between the RUL and the VAS ($r = 0.472$, $p = 0.0021$).

2. SDC and knee scores

The SDC values and the Lysholm scores were negatively correlated ($r = -0.501$, $p = 0.0003$), as were the SDC and the JKOM ($r = -0.605$, $p < 0.0001$). A significant positive correlation was found between the SDC and the VAS ($r = 0.541$, $p = 0.0003$; Fig. 2).

Contour irregularity and clinical assessments of each K/L group

The RUL tended to rise as the K/L grade increased, but no significant difference was observed between the K/L I and II and the K/L II and III. The SDC also tended to rise as the K/L grade increased, but no significant difference was observed between the K/L II and the K/L III. As for clinical assessments, the Lysholm score, VAS, and the JKOM tended to change according to the K/L grading, but only the K/L I and the K/L IV showed significant difference in all the three assessments (Table 1).

Correlation between MRI findings and histopathological examination

Derangements of the architecture of the trabeculae bones and cystic lesions were observed in the subchondral bone of the MFC in all nine cases used for histochemical

Table 1 Irregularities and clinical scores of each K/L grade

Average +/-standard deviation

	RUL	SDC	Lysholm score	VAS	JKOM
K/L I	1.08+/-0.05 ns	1.16+/-0.33 *	35.9+/-10.2 ns	66.3+/-18.4 ns	60.1+/-7.1 ns
K/L II	1.13+/-0.07 ns	1.68+/-0.36 **	26.0+/-6.9 **	67.0+/-2.8 ns	50.5+/-12.0 ns
K/L III	1.16+/-0.07 **	1.73+/-0.48 **	22.8+/-10.7 ns	71.6+/-19.1 *	50.9+/-21.5 ns
K/L IV	1.31+/-0.13 **	2.52+/-0.78 **	20.2+/-6.1 ns	86.8+/-10.9 ns	36.6+/-16.2 ns

(**: $p < 0.01$, *: $p < 0.05$, ns: not significant)

K/L Kellgren and Lawrence grade, RUL ratio of the upper surface to the lower surface of the contour, SDC standard deviation of contour thickness, VAS visual analogue scale, JKOM the Japanese Knee Osteoarthritis Measure

examinations, whereas less formation of cystic lesions was seen in the LFC. Average density of cystic lesions was $7.6 \pm 4.4/10$ mm in the MFC and $1.6 \pm 1.6/10$ mm in the LFC. Representative H&E staining of subchondral bone of the MFC is shown in Fig. 3a. Correlation coefficients for density of cystic lesions and irregularity were as follows: RUL: $r=0.446$, $p<0.01$; SDC: $r=0.846$, $p<0.0001$. Thus, irregular contours and the numbers of cystic lesions were positively correlated (Fig. 3-b).

Discussion

Obtaining a reliable index that objectively reflects knee OA severity should be helpful for determining treatment options and may possibly be useful to assess the efficacy of interventions. Evaluation based on imaging of affected joints is ideal, as it is not affected by the pathology of other joints that might obscure the results of an OA biomarker, such as in a urine or blood sample. Among several imaging technologies, radiographic examination is the most commonly used. However, the reliability for evaluating OA severity based upon radiographic findings is controversial.

Several studies showed that the radiographic features of knee OA were significantly associated with pain [12–14], whereas other studies have reported that OA severity based on radiographic findings was independent of pain [15, 16]. Many patients with relatively minimally damaged joints report knee pain [15]. In fact, we sometimes encounter a

discrepancy between the characteristic findings of OA on X-ray and the clinical severity of knee OA. Recently, MRI has increasingly been used to diagnose or evaluate OA.

The typical features that may have an association with joint pain are osteophytes [17], bone oedema [4] and synovitis [4, 18, 19]. However, the clinical importance of these findings has not as yet been confirmed [20–22]. Oedema in the subarticular bone marrow adjacent to the knee detected by T2-weighted MRI is associated with painful knee OA [4]. In contrast, a finding on MRI of subchondral bone oedema cannot satisfactorily explain the presence or absence of knee pain [20].

In this study, we focused on the MFC contour, which presumably corresponds to the subchondral bone of the MFC on MRI [7]. One of the radiographic features of OA is a sclerotic change of subchondral bone. Sclerotic lesions are a mixture of thin and thick subchondral bone as OA becomes more severe. In our previous study, the cystic lesions of sclerotic lesions were positively stained with antibodies against pain-related molecules, including cyclooxygenase-2 (COX-2) and tumour necrosis factor alpha (TNF- α) [23]. Thus, we speculated that the subchondral bone of the affected compartment could be a source of pain, and that the extent of corresponding pathological changes that occurred in subchondral bone could be assessed by newly developed software presented in this paper.

Our previous pilot study showed that irregularity of the MFC on MRI was correlated with knee scores [8]. In this

Fig. 3 Relationship between density of cystic lesions and irregularity. **a** Representative haematoxylin and eosin (H&E) staining of subchondral specimen retrieved at total knee arthroplasty (TKA) showed multiple formations of cystic lesions. **b** Density of cystic lesions and irregularity calculated according to preoperative magnetic resonance imaging (MRI) [standard deviation of the contour thickness (SDC)] are positively correlated

study, we present the possibility that RUL and SDC scores, which represent the irregularity of the MFC on MRI, could serve as indicators for disease severity in medial-type OA because the values of these two parameters increased as the Lysholm score and the JKOM decreased and as the VAS went up. Furthermore, these two parameters are positively correlated with the number of cystic lesions involved with the subchondral bone plate or the calcified zone. In this study, four parameters were initially employed, as the dependence upon only one or two values might miss detecting different types of irregular changes of the MFC. However, the ATC and the ASTC, which are related to changes in thickness, were far from being reliable. This was probably because a slight inconsistency in reproducing a black-and-white image during the process of conversion significantly affected these two parameters, especially the ASTC. We focused our attention on the femoral condyle and not on the tibial side in this study. There was a strong correlation between femoral and tibial cartilage volumes in the medial and lateral tibiofemoral joints both in subjects

with normal knees and those with radiological OA [24]. Changes to the femur were sensitive enough, and for that reason, the femoral side was selected.

There are many methods for treating OA, from nonsurgical treatments such as nonsteroidal anti-inflammatory drugs, disease-modifying osteoarthritis drugs, rehabilitation and insoles, to surgical treatments such as arthroscopic debridement, osteotomy, arthrodesis, knee arthroplasty and others [25]. Choosing a treatment option is often difficult because there is no reliable objective index. Our next goal is to use this assessment system when selecting treatment options. For now, we can only say that when an irregularity of the MFC becomes large, TKA would be the only treatment, because a field of pain-generation area (i.e., COX-2 and TNF- α -positive subchondral bone area) will be removed at the time of TKA, so that treatments such as an arthroscopic technique or osteotomy to preserve these areas would fail. Further study will enable us to select suitable treatments based on the RUL and SDC values.

One of the limitations of this study relates to image accuracy. For high-quality image acquisition, three-dimensional techniques may be required, such as spoiled gradient-echo sequences [26] that would produce more reliable indices. Second, subjects in this study had apparent knee OA on X-ray. This technique is not useful for patients in the early stage of OA who only have cartilaginous damage and thus have no remarkable changes on X-ray. When evaluating these patients, other MRI protocols that can detect hyaline cartilage, such as T2 maps at 3 T [27] or contrast-material-enhanced techniques [26] have to be used. The problem with those methods is that they are too time consuming for daily clinical use where acquisition time is limited per patient. FSE proton density is the primary pulse sequence for MRI of the knee joint and is one of the suggested protocols in clinical work [28]. It only requires a short time for acquisition, so we routinely use those images in daily clinical work, and they were employed in this study.

Although MRI is a rather expensive investigation for assessment of OA severity, the assessment of contour irregularity could be a useful tool for patients when normal radiographs are not conclusive.

Conclusion

New computer software that assesses irregularity of the MFC contour is useful for evaluating medial-type OA knees. Objective values derived from this software are closely associated with knee scores and can be used as an indication for determining treatment options.

Acknowledgments This study was funded by Comprehensive Research on Aging and Health, Health and Labor Sciences Research Grants of Japan.

Disclosures None.

References

- Kellgren J, Lawrence J (1957) Radiological assessment of osteoarthritis. *Ann Rheum Dis* 16:494–502
- Szebenyi B, Hollander AP, Dieppe P, Quity B, Duddy J et al (2006) Association between pain, function, and radiographic features in osteoarthritis of the knee. *Arthritis Rheum* 54:230–235
- Guermazi A, Zaim S, Tauli B, Miaux Y, Peterfy CG, Genant HG (2003) MR findings in knee osteoarthritis. *Eur Radiol* 13:1370–1386
- Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM et al (2001) The association of bone marrow lesions with pain in knee osteoarthritis. *Ann Intern Med* 134:541–549
- Dieppe P (1999) Subchondral bone should be the main target for the treatment of pain and disease progression in osteoarthritis. *Osteoarthritis Cartilage* 7:325–326
- Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S et al (2003) Bone marrow edema and its relation to progression of knee osteoarthritis. *Ann Intern Med* 139:330–336
- McGibbon CA, Bencardino J, Yeh ED, Palmer WE (2003) Accuracy of cartilage and subchondral bone spatial thickness distribution from MRI. *J Mag Reson Imaging* 17:703–715
- Iwasaki J, Sasho T, Nakagawa K, Ogino S, Ochiai N, Moriya H (2007) Irregularity of medial femoral condyle on MR Imaging serves as a possible indicator of objective severity of medial-type osteoarthritic Knee- a pilot study. *Clin Rheumatol* 10:1705–1708
- Lysholm J, Gillquist J (1982) Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *Am J Sports Med* 10:150–154
- Akai M, Doi T, Fujino K, Iwaya T, Kurosawa H, Nasu T (2005) An outcome measure for Japanese people with knee osteoarthritis. *J Rheumatol* 32:1524–1532
- Shibakawa A, Yudoh K, Masuko-Hongo K, Kato T, Nishioka K, Nakamura H (2005) The role of subchondral bone resorption pits in osteoarthritis: MMP production by cells derived from bone marrow. *Osteoarthritis Cartilage* 13:679–687
- Lethbridge-Cejku M, Scott WW Jr, Reichle R, Ettinger WH, Zonderman A, Costa P et al (1995) Association of radiographic features of osteoarthritis of the knee with knee pain: data from the Baltimore Longitudinal Study of Aging. *Arthritis Care Res* 8:182–188
- Boegard T, Rudling O, Petersson IF, Jonsson K (1998) Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. *Ann Rheum Dis* 57:401–407
- Boegard T, Rudling O, Petersson IF, Jonsson K (1998) Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the patellofemoral joint. *Ann Rheum Dis* 57:395–400
- Hannan MT, Felson DT, Pincus T (2000) Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. *J Rheumatol* 27:1513–1517
- Meding JB, Ritter MA, Faris PM, Keating EM, Harris W (2001) Does the preoperative radiographic degree of osteoarthritis correlate to the results in primary total knee arthroplasty? *J Arthroplasty* 16:13–16
- Creamer P (2000) Osteoarthritis pain and its treatment. *Curr Opin Rheumatol* 12:450–455
- Bollet AJ (2001) Edema of the bone marrow can cause pain in osteoarthritis and other diseases of bone and joints. *Ann Intern Med* 134:591–593
- Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME et al (2001) Knee effusions, popliteal cysts, and synovial thickening: association with knee pain in osteoarthritis. *J Rheumatol* 28:1330–1337
- Sowers MF, Hayes C, Jamadar D, Capul D, Lachance L, Jannausch M et al (2003) Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee osteoarthritis. *Osteoarthritis Cartilage* 11:387–393
- Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N et al (2003) Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. *Radiology* 226:373–381
- Garnero P, Ayral X, Rousseau JC, Christgau S, Sandell LJ, Dougados M et al (2002) Uncoupling of type 2 collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis. *Arthritis Rheum* 46:2613–2624
- Ogino S, Sasho T, Nakagawa K, Suzuki M, Yamaguchi S, Higashi M et al (2009) Detection of Pain-related molecules in the subchondral bone of osteoarthritic knees. *Clin Rheumatol* (in press)
- Cicuttini FM, Wluka AE, Stuckey SL (2001) Tibial and femoral cartilage changes in knee osteoarthritis. *Ann Rheum Dis* 60:977–980
- Felson DT, Lawrence RC, Hochberg MC, McAlindon T, Dieppe PA, Minor MA et al (2000) Osteoarthritis: new insights. Part 2: treatment approaches. *Ann Intern Med* 133:726–737
- Recht MP, Piraino DW, Paletta GA, Schils JP, Belhobek GH (1996) Accuracy of fat-suppressed three-dimensional spoiled gradient-echo FLASH MR imaging in the detection of patellofemoral articular cartilage abnormalities. *Radiology* 198:209–212
- Mosher TJ, Dardzinski BJ, Smith MB (2000) Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2-preliminary findings at 3 T. *Radiology* 214:259–266
- Math KR, Schneider R, Pavlov H, Ghelman B (2001) Imaging of the knee. In: Insall JN, Scott WN (eds) *Surgery of the knee*, 3rd edn. Elsevier Science, Philadelphia, pp 122–139