Relationship Between Pain Severity and Magnetic Resonance Imaging Features in Patients with Osteoarthritis of The Knee

Diz Ağrılı Hastalarda Manyetik Rezonans Görüntüleme Bulguları ve Ağrı Şiddeti Arasındaki İlişki

Ayhan Bilgici[1], Cengizhan Doğan[1], Erhan Çil[1], Şükran Sakarya[1], Ömer Kuru[1], Mustafa Bekir Selçuk[2]

[1]Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Fizik Tedavi ve Rehabilitasyon Anabilim Dalı, Samsun, Turkey

[2]Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Radyoloji Anabilim Dalı, Samsun, Turkey

Abstract

Objective: To evaluate the association between clinical symptoms and magnetic resonance imaging (MRI) findings in patients with osteoarthritis (OA) of the knee.

Materials and Methods: Ten men and 24 women between 30 and 60 years of age, who fulfilled the American College of Rheumatology (ACR) criteria for knee OA, were included in the study. All patients underwent MRI of the more symptomatic knee and the MRI findings were evaluated by the same radiologist blinded to clinical findings, using a semi-quantitative whole-organ MRI scoring method (WORMS). The Western Ontario and Mc-Master University (WOMAC) osteoarthritis index was used to assess physical function, morning stiffness, and joint pain.

Results: Linear regression analysis revealed that the total WORMS score and effusion severity were the most important predictors of the WOMAC pain score. The volume of the effusion was significantly correlated with the WOMAC pain and disability scores (r=0.601, p<0.001; and r=0.626 p<0.001, respectively). There was also a positive correlation between the WOMAC pain score and the WORMS bone marrow edema (BME) score (r=0.508, p<0.01).

Patients with synovial effusions had significantly higher WOMAC pain and disability scores compared to patients without synovial effusions (p<0.01 and p<0.001, respectively). Similar results were also observed in patients with BME compared to those without edema.

Conclusion: Our results demonstrated that the severity of synovial effusion on MRI was associated with increased pain and disability in knee OA. MRI allows the precise visualization of joint structures, such as cartilage, bone, synovium, ligaments, and menisci, so that the joint can be examined as a whole organ.

(Turk J Rheumatol 2010; 25: 184-90)

Key words: Knee, osteoarthritis, pain, Magnetic resonance imaging, WOMAC, WORMS

Received: 05.02.2009 **Accepted:** 08.06.2009

Özet

Amaç: Diz ağrılı hastalarda klinik semptomlar ve manyetik resonans görüntüleme (MRG) bulgularının birlikteliğini değerlendirmektir.

Yöntem ve Gereçler: 30-60 yaş arası, diz osteoartriti (OA) için Amerikan Romatoloji Birliği (ACR) kriterlerini karşılayan 10 erkek, 24 kadın hasta alındı. Hastaların tümünde daha semptomatik olan dizin MRG'leri alındı. MRG'lerinin tümü hastaların kliniğini bilmeyen bir radyolog tarafından değerlendirildi. MRG'leri semiquatitative whole organ skorlama metodu (WORMS) ile değerlendirildi. Fonksiyon, sabah tutukluğu ve eklem ağrısı için Western Ontario ve Mc-Master University osteoarthritis (WOMAC) indeksi kullandık.

Bulgular: Lineer regresyon analizleri, total WORMS skoru ve effüzyon şiddetinin WOMAC ağrı skorunun en önemli belirleyicileri olduğunu gösterdi. Effüzyon şiddeti, WOMAC ağrı ve disabilite skorları ile anlamlı koreleydi (r=0,601 p<0.001, r=0.626 p<0,001). WOMAC ağrı ve kemik iliği ödemi (KİÖ) skorları arasında da pozitif bir korelasyon vardı (r=0.508 p<0.01). Sinoviyal effüzyonlu hastalar, effüzyonu olmayan hastalardan anlamlı olarak daha yüksek WOMAC ağrı ve disabilite skorlarına sahiptiler (p<0.01 ve p<0.001). Benzer sonuçlar KİÖ'si olan ve olmayan hastalar arasında da gözlendi.

Sonuç: Sonuçlarımız diz OA'inde sinoviyal efüzyon şiddetinin, artmış ağrı ve disabilite ile birlikte olduğunu gösterdi. MRG kartilaj, kemik, sinoviyum, ligamentler ve menisküsler gibi eklemi oluşturan yapıların doğru gözlenmesine ve böylece eklemin bütün bir organ gibi değerlendirilmesine izin verir.

(Turk J Rheumatol 2010; 25: 184-90)

Anahtar sözcükler: Diz, osteoartrit, ağrı, manyetik resonans görüntüleme, WOMAC, WORMS

Alındığı Tarih: 05.02.2009 **Kabul Tarihi:** 08.06.2009

This study has been presented in EULAR 2008 and has been published in the abstract book.

Address for Correspondence: Dr. Ayhan Bilgici, Ondokuz Mayıs Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, Samsun, Turkey Phone: +90 362 312 19 19 Fax: +90 362 457 60 41 E-mail: abilgici@yahoo.com

doi: 10.5152/tjr.2010.26

Introduction

Osteoarthritis (OA) is the most common joint disease worldwide, and the prevalence increases with age (1). Although OA is traditionally known as a disease of the hyaline cartilage, it affects all of the articular structures, such as subchondral bone, fibrocartilage, ligaments, capsule, and synovium (2-4). Knee X-rays that are widely used for the assessment of painful joints are ineffective in demonstrating early changes in the joint (5, 6).

Knee OA is the major cause of pain and disability (1, 2). The primary goals of disease management are reducing pain and improving functional status. The exact source of pain in OA is not fully understood (3-6). There is no clear association between symptoms and radiographic findings. While there may be changes in articular cartilage and subchondral bone in the radiographies of patients without pain, individuals without radiographic OA may have significant pain symptoms (4, 6-9). This shows that in addition to changes in cartilage and subchondral bone, other joint structures are also affected and that OA should be considered as an organ failure (10).

Magnetic resonance imaging (MRI) techniques which have been developed in recent years allow simultaneous evaluation of all joint structures, along with the evaluation of the early changes in the cartilage (10, 11).

In this study, we aimed to determine the relationship between the structural changes in the joint observed by MRI and pain and disability in patients with knee OA.

Materials and Methods

Thirty-four patients (24 women and 10 men) between 30 and 60 years of age, admitted with knee pain to our outpatient clinic and diagnosed with OA of the knee according to the American College of Rheumatology (ACR) criteria, were included in the study (12). Patients with a history of knee trauma, surgical intervention, inflammatory disease, acute or chronic infection, metabolic disease, and those who received an intra-articular injection within the last year were excluded. Patients with any contraindications for MRI evaluation were also excluded. In patients with bilateral complaints, the more painful knee was tested. Weight, height, and body mass index (BMI; kg/m^2) of the patients were recorded.

Pain, disability, and morning stiffness scores of the Western Ontario and Mc-Master University (WOMAC) OA index were used for the clinical assessment of the patients (13). Pain was also assessed by a 10 cm visual analog scale (VAS).

Anteroposterior radiographs of the knee were obtained in all patients. X-rays were staged using the Kellgren Lawrence system (14). Patients with stage 4 OA were excluded from the study.

Magnetic Resonance Imaging

Images were obtained by a 1.5 Tesla MRI system (Magnetom Symphony-Quantum; Siemens, Erlangen, Germany) using a knee coil. All X-rays and MR images were evaluated by a musculoskeletal radiologist blinded to the clinical condition of the patients. MRI evaluation was performed using the semi-quantitative whole organ MRI scoring (WORMS) method. A total of 14 regions, including the anterior, central, and posterior segments of the medial and lateral femur and tibia, as well as the medial and lateral patella, were assessed. Fourteen types of structural changes were recorded in these 14 regions: cartilage integrity, subarticular bone marrow (BM) edema, subarticular cysts, subarticular bone flattening, marginal ostophytes, medial-lateral meniscal tears, integrity of the anterior and posterior cruciate ligaments, integrity of the medial and lateral collateral ligaments, synovitis/effusion, loose body (joint mice), and periarticular cysts/bursitis (11). Cartilage structure (0, normal cartilage thickness and signal; 6, diffuse cartilage loss in >75% of the region), subarticular BM edema and cysts (0, absent; 3, in >50% of the region), subarticular flattening (0, mild concavity; 3, severe concavity), marginal osteophytes (0, absent; 6, large), ligament tears (0, absent; 1, present), meniscal tears (0, absent; 4, complete tear or degeneration), effusion severity (0, absent; 3, filling most of the synovial cavity), loose body (0, absent; 3, 3 or more), and synovial cyst/bursitis (1, normal; 3, significant increase in size) were scored. The sum of all scores was recorded as the" total WORMS score". Those with an effusion score of 0 were considered as "absence of effusion", and those with an effusion score of 1-3 were considered as "presence of effusion". The patients were classified similarly according to BM edema.

Statistical Analysis

Statistical analysis of the data was performed using SPSS-10.0 software. Linear regression analysis was performed to determine the variables affecting pain. A non-parametric Spearman correlation test was used for correlation analysis. Patients with or without BM edema and patients with or without effusion were compared by a t-test. Inter-group comparison according to effusion severity was performed by Kruskal-Wallis analysis of variance and comparison of group pairs was performed by a Mann-Whitney-U test with Bonferroni correction. The level of statistical significance was set at $p<0.05$ for linear regression, correlation analysis and Kruskal-Wallis analyses, and at $p<0.05/3=0.016$ for the Mann-Whitney U test with Bonferroni correction.

Results

The mean age of the patients was 49.79±9.91 years and the mean duration of disease was 4.03±3.28 years. The mean total WORMS score was 24.84±14.16. The demographic and clinical characteristics of the patients are presented in Table 1.

Age and BMI were positively correlated with subarticular flattening (r=0.416, p=0.014; and r=0.462, p=0.006, respectively). The WOMAC pain score was significantly positively correlated with WOMAC disability, WORMS meniscus, and effusion scores (r=0.716, p=0.001; r=0.45, p=0.01; and r=0.601, p=0.001, respectively). There was also a significant positive correlation between WOMAC disability and effusion scores (r=0.63, p=0.01).

Table 1. Clinical and radiographic features of the patients

	Mean±SD
Age (years)	49.79±9.91
Disease duration (years)	4.03±3.28
BMI (kg/m^2)	31.43±2.28
Total WORMS score	24.84±14.16
VAS pain	6.38±1.16
WOMAC pain score	8.32±1.90
WOMAC disability score	24.62±2.28
WOMAC morning stiffness (min)	23.53±1.92
Radiological grade (Kellgren-Lawrence)	n (%)
1	12 (35)
2	15 (44)
3	7 (21)

BMI: Body mass index, VAS: Visual analog scale, semi-quantitative whole-organ MRI scoring method (WORMS) WORMS: Whole organ magnetic resonance imaging scoring, SD: Standard deviation, WOMAC: Western Ontario McMaster Universities Osteoarthritis Index

A significant positive correlation was also observed between the WORMS BM edema score and the VAS and WOMAC pain scores (r=0.488, p<0.01; and r=0.508, p<0.01, respectively).

The WORMS meniscus score was positively correlated with cartilage, osteophyte, and total WORMS scores (r=0.565, p=0.001; r=0.519, p=0.002; and r=0.396, p=0.02, respectively). The results of correlation analysis between the MRI findings are presented in Table 2.

Linear regression analysis, in which the WOMAC pain score was the dependent variable and the others were independent variables, revealed that WOMAC disability, effusion, and total WORMS scores were significant determinants for the WOMAC pain score (p<0.001, p<0.01, and p<0.05, respectively; Table 3).

WOMAC morning stiffness score was only positively correlated with the total cartilage score, which was close to significance (r=0.33, p=0.57).

A significant strong correlation was found between effusion and BM edema (r=0.451, p<0.01). Synovial effusion was present in 8 of 10 patients with BM edema. On regression analysis, the BM edema scores, although close, did not reach a significant level as a determinant of pain (p=0.06 for VAS pain and p=0.05 for WOMAC pain). Synovial hypertrophy was noted in 8 of 24 patients with effusion. Ligament injury was not noted in any of the patients. Loose bodies were noted in 2 patients, Baker's cysts in 3 patients, and pes anserine bursitis in 4 patients. Synovial cysts were not observed in any of the patients.

When patients with or without BM edema were compared, WOMAC pain and disability scores were found to be significantly higher in patients with BM edema (p<0.001 and p<0.01, respectively). A similar significant difference was noted between patients with

Table 2. Correlations between the changes in the joint on magnetic resonance imaging

	WORMS cartilage	WORMS meniscus	WORMS flattening	WORMS osteophyte	WORMS subarticular cyst	WORMS effusion
Total WORMS	r=0.891 p<0.001	r=0.545 p<0.001	r=0.543 p<0.001	r=0.814 p<0.001	r=0.714 p<0.01	r=0.714 p<0.001
WORMS cartilage	NS	r=0.643 p<0.01	r=0.422 p<0.001	r=0.627 p<0.001	r=0.638 p<0.001	NS
WORMS meniscus	NS	NS	NS	r=0.519 p<0.01	NS	NS
WORMS flattening	NS	NS	NS	r=0.446 p<0.01	r=0.518 p<0.01	NS
WORMS osteophyte	NS	NS	NS	NS	r=0.318 p<0.01	NS
WORMS BM edema	NS	NS	NS	NS	NS	r=0.451 p<0.01

NS: Not significant, r: Correlation coeffient, WORMS: Whole organ magnetic resonance imaging scoring

Table 3. Determinants of WOMAC pain according to regression analysis

	β	SE	p value	95% CI
WOMAC disability	0.623	0.030	p<0.001	0.095-0.220
Effusion/synovitis severity	0.418	0.410	p<0.01	0.467-2.161
Total WORMS Score	0.624	0.121	p<0.05	0.434-0.038

CI: Confidence interval; SE: Standard error, p<0.05 significant, p: p<0.05 significantly different, β: Standardized partial correlation coeffient, CI: confidence interval

and without effusions (p<0.01 and p<0.001, respectively). Patients with moderate (8 patients) and severe effusions (5 patients) had significantly higher pain and disability scores compared to patients with mild effusions (7 patients; p<0.016 for each parameter).

Discussion

Knee OA is the major cause of pain and disability. However, there is little correlation between clinical symptoms and radiographic findings (6-8). Our cross-sectional study has demonstrated that the severity of effusion and total WORMS score were the significant determinants of knee pain. Although the severity of BM edema did not reach statistical significance as a pain determinant, we found a significant positive correlation between pain and BM edema.

Although OA is the most frequent cause of joint pain, the pathophysiology of pain has not been fully understood (2, 3, 15). Progressive cartilage destruction, observed as joint space narrowing on direct radiographies in later stages, is the most significant feature of OA (9, 16). Due to the lack of vascularization and innervation of articular cartilage, it is difficult to explain osteoarthritic pain by cartilage destruction (3, 17-20). It is likely that other joint structures, such as bone, sinoviyal tissue, capsule, ligaments, and menisci, may be the source of pain in patients with OA. The fact that the essential changes in OA occur particularly in the subchondral bone, which has a rich innervation network, suggests that these changes in the subchondral bone may be the main source of pain (2, 3, 15, 21).

Cartilage destruction and reduction of its thickness leads to a decrease in its load-bearing capacity and an increase in friction. This, in turn, reduces the protection of subchondral bone, which is supported by cartilage (9, 21, 22). The increase in stress transfer to the subchondral bone leads to trabecular thickening. The increase in bone density further increases the physical stress on subchondral bone and bone marrow. This process results in increased stiffness of subchondral bone, flattening of the articular surface, and bone edema (4, 6, 23). In a cross-sectional study involving 143 patients, Torres et al. (24) found that the severity of knee pain was correlated with flattening, BM edema, meniscal tears, and effusions. Hernandez et al. (3) noted a significant correlation between the presence of knee pain and flattening (OR, 3.3; 95% CI, 2.5-4.5) in a recent study involving a Framingham OA cohort of 1627 patients. They have also reported that there is co-existing significant bone flattening and BM edema in 73% of the painful knees. The effect of flattening on pain did not reach statistical significance in our study (p=0.07). However, a significant positive correlation was noted between flattening and cartilage and osteophyte scores. Similar to our results, Nagaosa et al. (25) also showed that there is a significant association between flattening and osteophyte size. This suggests that flattening occurs as a consequence of changes in bone remodeling and cartilage destruction, in response to mechanical stress. The positive correlation between flattening and BMI also supports the role of mechanical stress in knee OA. In a 24-month follow-up study involving 107 patients, Pelletier et al. (26) found that high baseline BMI was a significant risk factor for the loss of cartilage volume determined by MRI of the medial knee compartment.

Periostal bone and BM, both having a rich nociceptive network, are the other potential sources of pain in OA. BM lesions and subchondral changes are often located below the lesion in the cartilage (4, 6). However, the effects of changes in subchondral bone on cartilage damage are not clear. Initially, it has been suggested by Radin and Rose (27) that an increase in subchondral bone stiffness may lead to cartilage destruction. Later, long-term follow-up studies have demonstrated that changes in the subchondral bone and BM edema observed in the early stages, are the main determinants of progression in OA (6, 28). We found a positive correlation between cartilage score and flattening and BM edema. This suggests that changes in the cartilage and bone occur simultaneously.

In a cross-sectional study, Felson et al. (17) found that BM edema was noted on MRI in 77.5% of the patients with knee pain. They reported a significant association between lesion size and pain (OR, 3.31; 95% CI, 1.54-7.41). They observed BM edema in 48% of the patients at stage 0 and in 100% of those at stage 4, according to Kellgren-Lawrence system. BM edema rates were lower in our study (30%). This might be explained by the fact that patients at stage 4 were not included in the study.

A possible explanation for the mechanism underlying BM edema, can be summarized as an increase in traumatic loading of the bone due to the reduction in cartilage thickness and an increase in subchondral bone stiffness. Local subchondral microfractures, inflammation, and edema occurs as a result of this process (4, 9, 21). Following bone injury, the lesion region fills with blood,

water, and other extracellular fluids. Bloody BM is slowly replaced by fatty and fibrotic BM. Non-specific necrosis, fibrosis, and trabecular abnormalities have been noted on histologic examination of the BM edema (9, 23, 27, 29). Another theory is the formation of cavitation within the trabecular bone similar to the formation of subchondral cysts as a result of pumping of the synovial fluid to subchondral BM through the cartilage and bone defects. Impairment of venous drainage in the BM results in an increase in interosseous pressure and pain (6, 17). The association of transient BM edema of the hip with pain also supports the hypothesis that this lesion is the source of pain (23, 28). Conversely, Sowers et al. (6) have found that BM edema findings were similar in patients with radiographic OA who did or did not have pain. However, they found that full-thickness cartilage and neighboring subchondral bone defect on MRI was significantly more common in patients with pain. We noted significantly higher pain and disability scores in patients with BM edema compared to those without edema.

Another potential source of knee pain might be synovitis/effusion, which leads to distention of the highly innervated capsule. Low-grade effusion accompanied by synovial thickening has been defined in 75% of osteoarthritic knees (3). Hill et al. (30) noted moderate-to-high effusions by MRI in 56.4% of the patients with knee pain and radiographic OA. Similar to our results, they also noted a significant correlation between pain and the presence and amount of effusion. Song et al. (31) found effusions on MRI in 61% of patients with knee OA while the rate of patients with effusions was 85% in the study conducted by Tarhan et al. (32). We found effusions in 58% of patients. The effusion severity was found to be the most significant determinant of pain. This finding suggests that pain intensity is proportionally increased by the amount of distention in the joint capsule.

Meniscal lesions are common in patients with OA. The role of meniscal tears on pain and functional disability is controversial. The prevalence of meniscal damage noted on MRI in symptomatic knee OA has been reported as 52%-92% in previous studies (9, 27, 33, 34). Bhattacharyya et al. (15) compared the MR images of patients with symptomatic knee pain and asymptomatic controls and found no significant difference between the groups in terms of pain and disability scores, and they noted meniscal tears in 67% of asymptomatic patients. Meniscal lesions were observed in 47% of our patients. The positive correlation between pain and meniscal damage may be interpreted as an increase in pain as the meniscal damage reaches to the fibers located in the outer one-third region of the meniscus. We also found a significant correlation between meniscal damage and cartilage destruction. In their 2-year follow-up study, Berthiaume et al. (34) found that volume loss was greater in the medial cartilage in patients with advanced medial meniscal tears. These results are supportive of the meniscal functions, including distribution of axial loading, protection of the neighboring cartilage, and stabilization of the joint.

The association between pain and osteophytes is also controversial. Boegard et al. (35) found a positive correlation between pain and osteophytes located at the medial femoral condyle observed on knee X-rays obtained at semiflexion position. However, in their study, including patients with chronic pain, these authors did not provide the details of the methods they used for pain assessment. Osteophytes are formed in the joint, as a proliferative response to inflammation of the neighboring synovial membrane or distention of the joint capsule, which gradually lose its stability with aging. Marginal osteophytes may become painful due to their close interaction with the synovium and joint capsule (9, 35). We did not find a correlation between pain and osteophyte scores. This might be due to presence of osteophytes in the later stages of OA. There were few patients at stage 3 and no patients at stage 4 in our study population. It has also been reported that osteophytes have a high positive predictive value for cartilage defects, as determined by MRI (9). We noted that osteophyte scores were significantly correlated with cartilage and meniscus damage. This suggests that changes in the articular cartilage, meniscus, and bone play a significant role in the development of osteophytes (9, 36).

Subchondral cysts are fluid-filled cavities and are often associated with joint space narrowing and sclerosis. The pathogenesis has been explained as the entrance of synovial fluid into subchondral bone subsequent to cartilage destruction. As the cyst is surrounded by fibrous tissue, the relation with the joint space is terminated (6, 10). Our finding of an association between subchondral cyst formation and cartilage destruction, osteophyte formation, and flattening is supportive of this hypothesis.

Our results suggest that the total WORMS score and severity of the effusion are the most significant determinants of pain. Along with the results of previous studies, our findings indicate that the source of osteoarthritic pain is multifactorial. OA is a disease in which changes in the cartilage, bone, and synovial tissue play a role. Genetic, metabolic, and cultural factors may also play a significant role in structural damage. MRI is a non-invasive method which allows comprehensive assessment and detection of early structural changes in osteoarthritic joints.

Conflict of Interest

No conflict of interest declared by the authors.

References

1. Felson DT, Naimark A, Anderson JJ, Kazis L, Castelli W, Meenan RF. The prevalence of knee osteoarthritis in the elderly:The Framingam Osteoarthritis Study. Arthritis Rheum 1987; 30: 914-8.
2. Felson DT. The sources of pain in knee osteoarthritis. Curr Opin Rheumatol 2005; 17: 624-8.
3. Hernandez-Molina G, Neogi T, Hunter DJ, Niu J, Guermazi A, Reichenbach S, et al. The association of bone attrition with knee pain and other MRI features of osteoarthritis. Ann Rheum Dis 2008; 67: 43-7.
4. Pessis E, Drape JL, Ravaud P, Chevrot A. Assessment of progression in knee osteoarthritis: results of a year study comparing arthroscopy and MRI. Osteoarthr Cartilage 2003; 11: 361-9.
5. Hunter DJ, Felson DT. Osteoarthritis. Clinical Review BMJ 18; 332: 639-42.
6. Sowers MF, Hayes C, Jamadar D, Capul D, Lachance L, Jannausch M, et al. Magnetic resonance-detected subchondral bone marrow and cartilage defect characteristics associated with pain and X-ray-defined knee. Osteoarthr Cartilage 2003; 11: 387-93.
7. Felson DT. Epidemiology of knee osteoarthritis: results from the Framingam Osteoarthritis Study. Semin Arthritis Rheum 1990; 20: 42-50.
8. Hodler J, Resnick D. Current status of imaging of articular cartilage. Skeletal Radiol 1996; 25: 703-9.
9. Link TM, Steinbach LS, Ghosh S, Ries M, Lu Y, Lane N, et al. Osteoarthritis: MR imaging findings in different stages of disease and correlation with clinical findings. Radiology 2003; 226: 373-81.
10. Guermazi A, Zaim S, Taouli B, Miaux Y, Peterfy CG, Genant HG. MR findings in knee OA. Eur Radiol 2003; 13: 1370-86.
11. Peterfy CG, Guermazi A, Zaim S, Tirman PF, Miaux Y, White D, et al. Whole-Organ magnetic resonance imaging score (WORMS) of the knee in osteoarthritis. Osteoarthr Cartilage 2004;12: 177-90.
12. 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: 1039-49.
13. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol 1988; 15: 1833-40.
14. Kellgren JH, Lawrence JS. Radiologic assessment of osteoarthritis. Ann Rheum Dis 1957; 16: 494-502.
15. Bhattacharyya T, Gale D, Dewire P, Totterman S, Gale E, McLaughlin S, et al. The clinical importance of meniscal tears demonstrated by magnetic resonance imaging in osteoarthritis of the knee. J Bone Joint Surg 2003; 85: 4-9.
16. Jones G, Ding C, Scott F, Glisson M, Cicuttini F. Early radiographic osteoarthritis is associated with substantial changes in cartilage volume and tibial bone surface area in both males and females. Osteoarthr Cartilage 2004; 12: 169-74.
17. Felson DT, Chaisson CE, Hill CL, Totterman SM, Gale ME, Skinner KM, et al. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Intern Med 2001;134: 541-9.
18. Wluka A, Wolfe R, Stuckey S, Cicuttini F. How does tibial cartilage volume relate to symptoms in subjects with knee osteoarthritis? Ann Rheum Dis 2004; 63: 264-8.
19. Kornaat P, Bloem J, Ceulemans R, Riyazi N, Rosendaal F, Nelissen R, et al. Osteoarthritis of the knee: association between clinical features and MR imaging findings. Radiology 2006; 239: 811-7.
20. Hunter DJ, March L, Sambrook P. The association of cartilage volume with knee pain. Osteoarthr Cartilage 2003; 11: 725-9.
21. Dieppe P. Subchondral bone should be the main target for the treatment of pain and disease progression in osteoarthritis. Osteoarthr Cartilage 1999; 7: 325-6.
22. Lindsey T, Narasimhan A, Adolfo JM, Jin H, Steinbach LS, Link T, et al. Magnetic resonance evaluation of the interrelationship between articular cartilage and trabecular bone of the osteoarthritic knee. Osteoarthr Cartilage 2004; 12: 86-96.
23. Bollet AJ. Edema of the bone marrow can cause pain in osteoarthritis and other disease of bone and joints. Ann Intern Med 2001; 134: 591-3.
24. Torres L, Dunlop D, Peterfy C, Guermazi A, Prasad P, Hayes K, et al. The relationship between specific tissue lesions and pain severity in persons with knee osteoarthritis. Osteoarthr Cartilage 2006; 14: 1033-40.
25. Nagaosa Y, Lanyan P, Doherty M. Characterization of size and direction of osteophyte in knee osteoarthritis: a radiographic study. Ann Rheum Dis 2002; 61: 319-24.
26. Pelletier JP, Raynauld JP, Berthiaume MJ, Abram F, Choquette D, Haraovi B et al. Risk factors associated with the loss of cartilage volume on weight-bearing areas in knee osteoarthritis patients assessed by quantitative magnetic resonance imaging: a longitudinal study. Arthritis Res Ther 2007; 9 :R74
27. Radin EL, Rose RM. Role of subchondral bone in the inition and progression of cartilage damage. Clin Orthop 1986; 213: 34-40.
28. Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale E, Totterman S, et al. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Intern Med 2003; 139: 330-6.
29. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in OA knees: correlation between MR imaging and histologic findings. Radiology 2000; 215: 835-40.
30. Hill C, Gale D, Chaisson C, Skinner K, Kazis L, Gale E, et al. Knee effusions, popliteal cysts, and synovial thickening. Association with knee pain in osteoarthritis. J Rheumatol 2001; 28: 1330-7.
31. Song IH, Burmester GR, Backhaus M, Althoff CE, Hermann KG, Scheel AK, et al. Knee osteoarthritis. Efficacy of a new method of contrast-enhanced musculoskeletal ultrasonography in detection of synovitis in patients with knee osteoarthritis in comparison with magnetic resonance imaging. Ann Rheum Dis 2008; 67: 19-25.

32. Tarhan S, Unlu Z. Magnetic resonance imaging and ultrasonographic evaluation of the patients with knee osteoarthritis: a comparative study. Clin Rheumatol 2003; 22: 181-8.
33. Fukuta S, Masaki K, Korai F. Prevalence of abnormal findings in magnetic resonance images of asymptomatic knees. J Orthop Sci 2002; 7: 287-91.
34. Berthiaume MJ, Raynauld JP, Martel-Pelletier J, Labonte F, Gilles B, Bloch DA, et al. Meniscal tear and extrusion are strongly associated with the progression of knee osteoarthritis as assessed by quantitative magnetic resonance imaging. Ann Rheum Dis 2005; 64: 556-63.
35. Boegard T, Rudling O, Petersson IF, Jonsson K. Correlation between radiographically diagnosed osteophytes and magnetic resonance detected cartilage defects in the tibiofemoral joint. Ann Rheum Dis 1998; 57: 401-7.
36. McCauley TR, Kornaat PR, Jee WH. Central osteophytes in the knee: prevalence and association with cartilage defects on MR imaging. AJR 2001; 176: 359-64.