WorldCare Clinical
A ProScan Imaging Company

The WCC Note™

Reported by Margaret D. Phillips, M.D.; Presented by Stephen J. Pomeranz, M.D.

www.wcclinical.com / +1 617-250-5143 Your Weekly Guide To Harmonizing Clinical Trial Imaging

Volume 3, Number 10 – December 3, 2009

Knee Osteoarthritis: MRI in the Landscape of Current and Potential Treatment

Like trying to mend broken glass in the hope that it will shine clearly again, repairing the destruction of knee osteoarthritis (OA) looms as an arduous and complex task – if it could ever be accomplished.

Where is current science, then, on the path to one day preventing, arresting, or reversing this debilitating crippler of joints? This issue of *The WCC Note* continues our series on knee OA by examining current literature on treatment and prospective cures, and how MRI is poised to aid in monitoring the disease.

As outlined in previous issues of this newsletter, the enormity of knee OA as a population problem – the scope of its occurrence, pathogenesis, and heterogeneity – confounds a simplistic approach to therapy. Rather than a single disease-modifying drug, surgery, or physical therapy procedure, the idea that multiple influences lead to a common endpoint of joint destruction means that this multidimensional disease will, in most cases always require a multifaceted treatment approach.

While this can seem like a frustrating and daunting process, it helps to step back and tease apart the fundamental questions at hand, imposing structure on the analysis of this most labyrinthine of common disorders. ■

TREATMENT

What treatment approaches to knee OA are currently practiced?

1. A 2008 overview of knee osteoarthritis management in Rheumatic Disease Clinics of North America called for conservative treatment, outlining recommendations from the Task Force of the Standing Committee for International Clinical Studies including Therapeutic Trials (ESCISIT). (1, 2) In summary, the guidelines were:
   a. Combination nonpharmacologic and pharmacologic treatment.
   b. Treatment tailored according to risk factors, such as obesity and activity, age, level of pain, signs of inflammation, and location and extent of structural damage.
   c. Education, exercise, use of appliances, and weight reduction.
   d. Paracetamol (acetaminophen) as the first analgesic used and the preferred long-term choice if efficacy is established.
   e. Topical NSAIDs and capsaicin are efficacious and safe.
   f. NSAIDs can be considered in patients for whom paracetamol is not helpful. Nonselective NSAIDS or COX-2 inhibitors play a role for a subset of patients.

g. Opioid analgesics, with or without paracetamol, can be useful in patients for whom NSAIDs are contraindicated or do not work.

h. Symptomatic, slow-acting drugs such as avocado-soybean unsaponifiables may be of benefit.

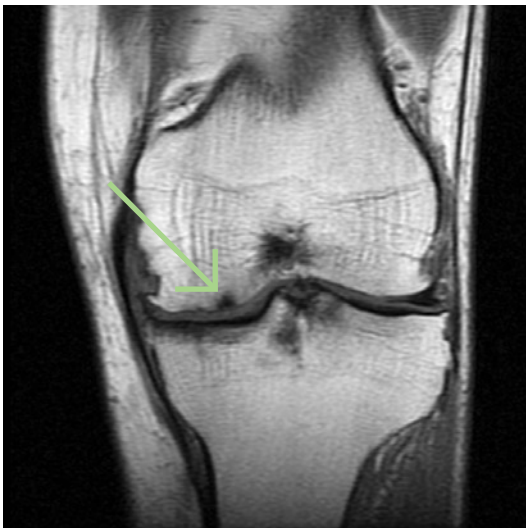
i. Intra-articular injection of long-acting corticosteroids may be useful in settings of pain flare.

j. Joint replacement becomes a consideration for patients with refractory pain and disability.

2. In the September 2009 *Journal of the American Academy of Orthopedic Surgery,* authors from The New England Baptist Hospital in Boston reported practice guidelines for knee OA that were developed explicitly aside from knee replacement (arthroplasty). The authors recommend that patients participate in educational programs regarding self-management, weight loss, exercise, and quadriceps strengthening. The guidelines recommend taping for short-term pain relief, analgesics, and intra-articular corticosteroids. The report advises against free-floating interpositional devices and lateral heel wedges for medial compartment knee OA. The authors note that the group did not come to a recommendation in regards to the use of braces with valgus- or varus-directing forces. (3)

OA & MENISCAL TEARS

Are meniscal tears caused by, or a result of, OA, and what does current literature advise about the role of surgery for them?



Coronal T1 weighted image. Arrow on full thickness grade IV chondromalacia. Also has osteophytes, truncated medial meniscus, and pseudocysts in the intertibial spine region. Mild medial femoral squaring and tibial plateau remodeling.

It is well known that normal menisci are rare in osteoarthritic knees. While meniscal lesions in healthy knees may result in osteoarthritis due to loss of meniscal function, osteoarthritis may itself lead to meniscal tears, which subsequently accelerate the disease. Proteolytic degradation and shear stress may lead to decreased meniscal tensile strength. Meniscal tears may then result from the compromised meniscus being unable to withstand loads and force transmitted during normal joint loading. (4)

Meniscal resection is reported as the procedure most frequently performed by orthopaedic surgeons in the United States. A recent review called for well-designed, randomized, controlled clinical trials to study the true effects of meniscal resection, repair or transplant, or nonsurgical treatments, as compared with placebo or sham treatment. (4)

Noting that a meniscal tear is an almost ubiquitous MRI finding in a person with knee arthritis and is not necessarily responsible for symptoms, Hunter and Low wrote in *Rheumatic Disease Clinics of North America* that the removal of menisci should not be performed unless there is clinical locking or extension blockade, since strong evidence supports that even partial meniscectomy increases the risk for worsening osteoarthritis. (1)

Allogenic, xenogenic, or artificial material meniscal replacements have been attempted in younger subjects post-total meniscectomy, but transplant survival is variable and long-term results prove lacking. (4)

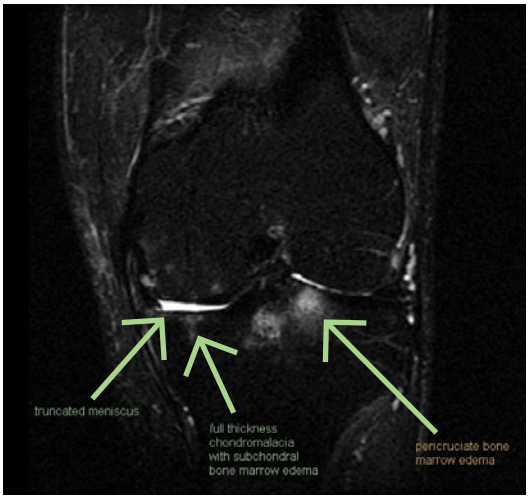
Individuals with initial asymptomatic meniscal lesions have a clinical course that shows an increased frequency of symptoms compared to those without meniscal lesions, though the pain and impairment remain of low severity. (5)

MRI T2 measurements of cartilage in patients with osteoarthritis show them to be increased in patients with meniscal tears. Friedrich, et al., note that this supports the theory of meniscal and hyaline cartilage damage occurring in the setting of osteoarthritis. (6)

SURGERY FOR KNEE OA

What surgical approaches exist, and what does recent literature report about them?

1. **Lavage and Debridement:** Arthroscopic lavage and debridement are not recommended for routine treatment, as they do not alter disease progression. (7) In a study involving 92 patients assigned to surgery (and six not undergoing surgery), as well as 86 controlled subjects who received only physical and medical therapy, arthroscopic surgery with surgical lavage and debridement failed to add additional benefit to patients with moderate to severe osteoarthritis over optimized physical and medical therapy. (8)
2. **Microfracture:** A technique for therapy of focal chondral defects, the microfracture surgical procedure involves subchondral drilling to create 4mm-deep pits, into which multipotential stem cells migrate from the subjacent marrow to form fibrocartilaginous tissue repair. (9)



Coronal SPIR showing truncated meniscus (LEFT ARROW), full-thickness chondromalacia with subchondral bone marrow edema (CENTER ARROW), and pericruciate bone marrow edema (RIGHT ARROW).

3. **Cell-Based Cartilage Repair:**
    a. *Autologous Chondrocyte Implantation (ACI):* In this procedure, chondrocytes are harvested from nonweight-bearing cartilage, cultured in vitro and subsequently reimplanted. Elegant reviews of the technique geared towards imaging were published in *Radiographics* in 2007 and 2008. (9,10) MRI can depict the state of cartilage healing, as well as the subchondral bone and bone marrow. (10)

    Noting that young individuals with early osteoarthritis who want to remain physically active have limited treatment options, ACI may offer benefit, according to Minas, et al., in a 2009 study. (11)

    ACI can be performed using a polymer-based graft to repair cartilage defects. While the ACI technique typically requires a rim of intact cartilage at the periphery of the defect, a recent report states that a newer technique can allow cartilage repair even when such a rim is not present. In general, the technique uses chondrocytes harvested from healthy cartilage in nonweight-bearing regions of the knee and transplants them into areas of defect. A report from 2009 states that chondrocytes cultivated in a three-dimensional matrix of bioresorbable material avoided the use of covering materials such as periosteum or collagen sheets. The fibrin polymer matrix provided a scaffold to stabilize the graft. The authors reported that improvements were still present four years after graft implantation for patients who had undergone the procedure. (12, 13)

    A 2009 study of symptomatic cartilage defects of the knee reported that chondrocyte implantation had better clinical outcomes at 36 months than the microfracture technique. (14)

    b. *Autologous Osteochondral Autograft Transplantation:* This technique harvests osteochondral plugs from the lateral femoral condyle or trochlear nonweight-bearing areas and transplants them into an area of articular defect. (9)

    c. *Osteochondral Allograft Implantation:* Osteochondral allograft transplantation involves the harvesting of cadaveric bone cartilage. (9)
4. **Osteotomy:** Osteotomy can be considered for unicompartmental knee OA, with the intent to shift the weight load away from the damaged compartment.
5. **Arthroplasty (Joint Replacement)**:
    a. Joint replacement surgery includes:
        i. Unicompartmental arthroplasty and patellofemoral replacement in selected patients with isolated medial or patellofemoral OA. (7)
        ii. Total knee arthroplasty for patients with severe OA.

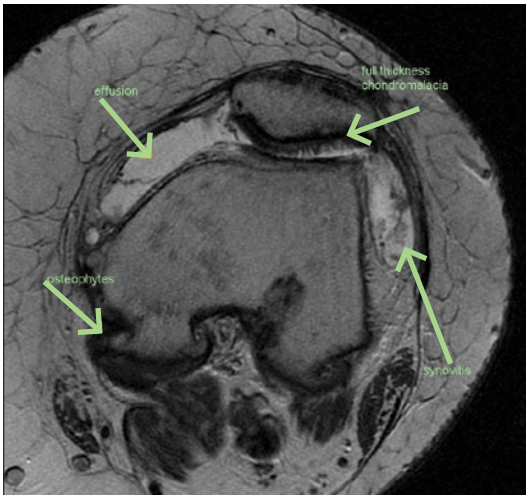
GLUCOSAMINE AND CHONDROITIN

Do glucosamine and chondroitin work?

Glucosamine and chondroitin sulfate, alone or in combination, failed to reduce pain effectively in a study of 1,583 patients with symptomatic knee osteoarthritis. The analysis suggested that the combination of both medicines may be of benefit to a subgroup of individuals who have moderate to severe knee pain. (15) Glucosamine, but not ibuprofen, has been shown to alter cartilage turnover in patients with osteoarthritis undergoing physical training. (16)

MRI AS BIOMARKER

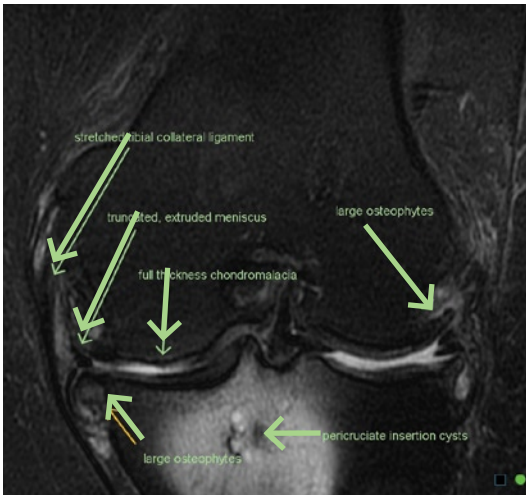
How can MRI be used to grade the impact of therapies – pharmaceutical, operative, physical therapy, and behavioral interventions?



Axial T2 weighted image showing (CLOCKWISE FROM LEFT) osteophytes, effusion, full-thickness chondromalacia, and synovitis.

1. MRI can provide semi-quantitative assessment in osteoarthritis because it can detail articular cartilage integrity; subchondral bone- marrow pathology; edema or cysts; subchondral bone attrition; marginally, centrally, and posteriorly positioned osteophytes; meniscal and ligament integrity; synovitis and effusion; and loose bodies. (17) Three commonly used whole-joint MRI imaging assessments are:
    a. Whole-organ MR imaging score (WORMS)
    b. Knee osteoarthritis scoring system (KOSS)
    c. Boston leads osteoarthritis knee score (BLOKS)
2. Cartilage can be reproducibly and accurately measured by MRI. (18) Cartilage morphology and trabecular bone may be quantitatively measured in the research arena to provide baseline and follow-up monitoring of treatment in OA. (19, 20) In a clinical trial, cartilage thickness can provide the same level of sensitivity as cartilage volume to estimate cartilage loss. (21)
3. MRI shows potential value as a biomarker, since studies have indicated that the presence of either bone-marrow lesions or meniscal disease is predictive of those OA patients at greater risk for disease progression. (22)
4. Very early changes in cartilage biochemistry, prior to joint damage or pain, may be able to be measured by experimental MRI methods of T1-rho and T2. (23)
5. Specialized research MRI protocols of T2 mapping, T1-rho, sodium MR, and delayed gadolinium-enhanced MRI imaging to assess the macromolecular status of cartilage may be useful in assessing disease-modifying strategies for OA. (24)
6. Molecular and functional techniques for imaging early osteoarthritis include charged-based methods such as delayed gadolinium-enhanced MRI of cartilage, which is based on the negatively charged T1-shortening agent gadopentetate dimeglumine. Hyaline cartilage has negatively charged molecules, similar in charge to gadolinium, and thereby repulses gadolinium when the cartilage is normal and intact. Conversely, damaged cartilage lacks the negatively charged hydrophilic molecules, allowing the gadolinium into the cartilage proper. (25)

7. Sodium-23 MR spectroscopy also takes advantage of the negative-fixed charged density (FCD) of cartilage. In this technique, sodium-23 atoms, which are positively charged, correlate directly with cartilage-fixed charged density. Sodium-23, therefore, decreases in abnormal cartilage. (25)
8. In the research arena, cathepsin B-sensitive near-infrared fluorescent probes have been used to image osteoarthritic knees in animals. Since damaged cartilage may release proteases such as cathepsins, this method is used experimentally to image matrix-degrading enzymes. (25)
9. Since OA is widely thought to result from local mechanical factors in people with systemic susceptibility, the influence of biomechanics in osteoarthritis, and the imaging quantification of them, is both interesting and important. Joint kinematics assessed with MRI imaging have been performed with patients supine in the magnet, with some recent work attempted in open-configuration scanners with vertical gaps, which allow standing. (26)



Coronal T2 fat suppressed image showing (COUNTER CLOCKWISE FROM UPPER LEFT) stretched tibial collateral ligament, truncated, extruded meniscus, full-thickness chondromalacia, large osteophytes, pericruciate insertion cysts, and large osteophytes. (Incidental note: Generalized tibial high signal is artifact from hardware.)

OA PROGRESSION

What have we learned about OA progression from MRI?

1. Patients with knee OA who display MRI evidence of meniscal damage or extrusion, as assessed by WORMS score, show association with cartilage loss over a 30-month period. (27, 18)
2. In a 2009 study from the Multicenter Osteoarthritis (MOST) study group (a longitudinal study of people with, or at high risk for, knee OA), those subjects who had minimal baseline cartilage damage but high body-mass index, meniscal damage, synovitis or effusion, or any baseline severe MRI lesion, had a strongly increased risk of fast cartilage loss. (28)
3. The finding of MRI-evident bone-marrow lesions (BMLS) shows association with change in knee cartilage over two years in asymptomatic subjects. As the size of the BMLS increases, there is increased progression of cartilage defects. The 2008 study included 271 healthy adults with no history of knee injury, knee pain, or clinical knee OA, who underwent knee MRI at baseline and two-year follow-up to study the relationship between presence of BMLS at baseline and cartilage change over two years. (29)
4. The role of alignment and biomechanics in osteoarthritis underwent review this year in Radiologic Clinics of North America. Valgus and varus malalignment were reported as increasing risk for OA, with patellar malalignment associated with patellofemoral OA progression. MR imaging measurements of kinematics, and measurements of contact area, were both discussed. (26)
5. The incidence of degenerative cleavage trizonal body tears in patients with moderate to advaced osteoarthritis is over 50 percent in patients over age 50 (personal observation by Dr. Stephen J. Pomeranz).

MRI IN OA CLINICAL TRIALS

What are some examples where MRI played a biomarker role in OA clinical pharmaceutical trials?

1. In patients with knee pain on efficacious doses of NSAIDs or acetaminophen, a decrease in effusion volume (quantified by gadolinium-enhanced T1 imaging) was observed and rapidly reversed when treatment was withdrawn. (30)
2. In a placebo-controlled, double-blind study of 377 knee OA patients, changes in MRI assessment of subchondral bone marrow abnormalities were observed within three month of treatment and were positively correlated with type II collagen degradation (determined by urinary CTX-II).

MRI imaging is a sensitive and early marker of OA that can correlate with drug efficacy.
(Contributed by Rick Walovitch, Ph.D., WorldCare Clinical)

CONCLUSION

Conclusion: **The complexity of knee osteoarthritis etiologies complicates the search for a single disease modifying therapeutic approach. Current treatment emphasizes conservative management including mechanical joint preservation measures. MRI depicts the whole joint nature of the disease and serves as a barometer of its time course.** ■

SOURCES

1. Hunter DJ, Lo GH. "The management of osteoarthritis: An overview and call to appropriate conservative treatment." *Rheum Dis Clin North Am,* 2008; 34:689-712.
2. Jordan KM, Arden NK, *et al.* "EULAR recommendations 2003: an evidence-based approach to the management of knee osteoarthritis: Report of a Task Force of the Standing Committee for International Clinical Studies including Therapeutic Trials (ESCISIT)." *Ann Rheum Dis,* 2003; 62:1150
3. Richmond J, Hunter D, *et al.* "Treatment of osteoarthritis of the knee (non-arthroplasty)." *J Am Acad Orthop Surg,* 2009 September; 17 (9):591-600.
4. Englund M, Guermazi A, *et al.* "The role of the meniscus in knee osteoarthritis: A cause or consequence?" *Radiol Clin North Am,* 2009; 47:703-712.
5. Zanetti M, Pfirrmann CWA, *et al.* "Clinical course of knees with asymptomatic meniscal abnormalities: Findings at two-year followup after MR imaging-based diagnosis." *Radiology,* 2005; 237:993-997.
6. Friedrich KM, Shepard T, *et al.* "T2 measurements of cartilage in osteoarthritis patients with meniscal tears." *Am J Radiol,* 2009; 193-W411-W415.
7. Lutzner J, Kaspen P, *et al.* "Surgical options for patients with osteoarthritis of the knee." *Nat Rev Rheumatol,* 2009; 5:309-316.
8. Kirkley A, Birmingham TB, *et al.* "A randomized trial of arthroscopic surgery for osteoarthritis of the knee." *N Engl J Med,* 2008; 359:1097-107.
9. Choi YS, Potter HG, *et al.* "MR imaging of cartilage repair in the knee and ankle." *Radiographics,* 2008; 28:1043-1059.
10. Ho YY, Stanley AJ, *et al.* "Postoperative evaluation of the knee after autologous chondrocyte implantation: What radiologists need to know." *Radiographics,* 2007; 27:207-222.
11. Minas T, Gomoll AH, *et al.* "Autologous chondrocyte implantation for joint preservation in patients with osteoarthritis." *Clin Orthop Relad Res,* Aug. 4, 2009 (e-published ahead of printing).
12. Price S. "Osteoarthritis. Autologous cartilage graft for OA: Stable four years on." *Nat Rev Rheumatol,* 2009; 5-234.
13. Kreuz PC, *et al.* "Treatment of focal degenerative cartilage defects with polymer-based autologous chondrocyte graft: Four-year clinical results." *Arthritis Res Ther 11,* R33 (2009).
14. Sais DB, Zanlauwe J, *et al.* "Treatment of symptomatic cartilage defects of the knee: Characterized chondrocyte implantation results in better clinical outcome of 36 months in a randomized trial compared to microfracture." *Am J Sports Med,* Oct. 21, 2009 (e-published ahead of printing).
15. Clegg DO, Reda DJ, *et al.* "Glucosamine, chondroitin sulfate, the two in combination for painful knee osteoarthritis." *N Engl J Med,* 2006; 354:795-808.
16. Petersen SG, Saxne T, *et al.* "Glucosamine but not ibuprofen altered cartilage turnover in osteoarthritis patients in response to physical training." *Osteoarthritis Cartilage,* Jul. 15, 2009 (e-published ahead of printing).
17. Roemer FW, Guermazi A. "MR imaging-based semiquantitative assessment in osteoarthritis." *Radiol Clin North Am,* 2009; 47:633-654.

18. Wenham CY, Conaghan PG. “Imaging the painful osteoarthritic knee joint: What have we learned?” *Nature Clinical Pract Rheumatol,* 2009; 5:149-158.
19. Eckstein S, Guermazi A, *et al.* “Quantitative MR imaging of cartilage and trabecular bone in osteoarthritis.” *Radiol Clin North Am,* 2009; 47:655-673.
20. Sharma L, Eckstein F, *et al.* Relationship of meniscal damage, meniscal extrusion, malalignment,and joint laxity to subsequent cartilage loss in osteoarthritic knees. *Arthritis Rheum* 2008; 58(6):1716-26.
21. Raynauld JP, Martel-Pelletier J, *et al.* “Analysis of the precision and sensitivity to change of different approaches to assess cartilage loss by quantitative MRI in longitudinal multicenter clinical trial in knee osteoarthritis patients.” *Arthritis Res Ther,* Nov. 5, 2008;10 (6):R129 (e-published ahead of printing).
22. Abramson SB, Attur M. “Developments in the scientific understanding of osteoarthritis.” *Arthritis Res Ther,* 2009:11-227. (Available online: http://arthritis-research.com/content/11/3/227).
23. Li X, *et al.* “In vivo T1 and T2 mapping of articular cartilage in osteoarthritis of the knee using 3T MRI.” *Osteoarthritis Cartilage* 2007; 15:789-797.
24. Burstin D, Gray M, *et al.* “Measures of molecular composition and structure in osteoarthritis.” *Radiol Clin North Am,* 2009; 47:675-686.
25. Biswal S, Resnick DL, *et al.* “Molecular imaging: Integration of molecular imaging into the musculoskeletal imaging practice.” *Radiology,* 2007; 244:651-666.
26. Hunter DJ, Wilson DR. “Role of alignment and biomechanics in osteoarthritis and implications for imaging.” *Radiol Clin North Am,* 2009; 47:553-566.
27. Hunter DJ, Zhang YQ, *et al.* “The association of meniscal pathologic changes with cartilage loss in symptomatic knee osteoarthritis.” *Arthritis Rheum,* 2006; 54:795-801.
28. Roemer FW, Zhang Y, *et al.* “Tibiofemoral joint osteoarthritis: Risk factors for MR-depicted fast cartilage loss over a 30-month period in the multicenter osteoarthritis study.” *Radiology,* 2000; 252:772-780.
29. Wluka AE, Wang Y, *et al.* “Bone marrow lesions predict progression of cartilage defects and loss of cartilage volume in healthy middle-aged adults without knee pain over two years.” *Rheumatology,* 2008; 47:1392-6 (e-published Jul. 7, 2008).
30. Brandt KD, Mazzuca SA, Buckwalter KA. “Acetaminophen, like conventional NSAIDs, may reduce synovitis in osteoarthritic knees.” *Rheumatology,* 2006; 45:1389-1394.

WorldCare Clinical
A ProScan Imaging Company
Conducting clinical trials imaging in perfect harmony.

THE WCC NOTE™: Volume 3, Number 10 – December 2, 2009
- *Research and Reporting:* Margaret D. Phillips, M.D. (newsletter@wcclinical.com)
- *Reviewer and Publisher:* Stephen J. Pomeranz, M.D. (newsletter@wcclinical.com)
- *Managing Editor:* Shannon Roeper
- *WorldCare Clinical Editorial Advisors:* Richard C. Walovitch, Ph.D.; Vanessa Conde
- *Graphic Designer:* Tom Anneken