Knee Osteoarthritis: MRI in the Landscape of Current and Potential Treatment PART 2

Patients with knee osteoarthritis (OA) will likely not all be cured by the same treatment. Rather than a simple binary switch to turn off the disease or unwind its damage, an algorithm of approaches will probably always be needed. This final installment of The WCC Note on osteoarthritis continues a discussion of OA treatments, those currently used and possibilities for the future, and the place of MRI in that equation.

What features of OA correlate with pain? Do people have imaging findings of OA without symptoms?

1. According to a 2009 review of pain in osteoarthritic knees published in Nature Clinical Practice Rheumatology, the cause of pain in osteoarthritis is not fully understood. (1)

2. Since knee pain has shown association to synovial hypertrophy, synovial effusions, and subchondral bone abnormalities in large cohort studies, MRI is increasingly being used to correlate between symptoms and structural findings. (1) Imaging may also show changes of OA in people without symptoms, with Link et al reporting MRI findings in osteoarthritis and Kellgren-Lawrence score not significantly correlating with clinical pain, stiffness, and function limitation. (2)

3. The structural changes associated with osteoarthritis that can be depicted by MRI in patients with no knee symptoms include effusion, cartilage defects, and bone marrow lesions (BML). While bone marrow edema-like lesions (BML) prove not diagnostic for OA, as they can be seen in such conditions as rheumatoid arthritis or trauma, the incidence of BML increases as the radiographic Kellgren-Lawrence (K/L) grade increases. The subchondral bone, which is well evaluated by MRI, has robust innervation and is thought to be important as an etiology of osteoarthritis pain. (1)
4. Synovitis occurs from the earliest stages of OA. Effusion and synovial hypertrophy happen significantly more often in painful knees compared to asymptomatic ones. (1)

5. Knee pain results with medial tibial chondral defects and BMLs, but not with radiographic knee OA according to Zhai et al. (3)

6. According to Torres et al, pain severity correlates positively with MRI BML, meniscal tears, synovitis and effusion, and bone attrition (4).

7. In a study by Kornatt et al of 205 people with multiple joint symptomatic OA, OA knee pain was associated with a large joint effusion or presence of patellofemoral compartment osteophyte, but not other MRI imaging findings such as cartilage abnormality, subchondral cyst, bone marrow edema, subluxed meniscus, meniscal tears, or Baker’s cysts. (5)

8. Disparity exists between plain film findings and symptoms, as reviewed by Wenham and Conaghan. Previously, the Kellgren-Lawrence grading system of radiographic OA quantification found widespread use. The radiographic findings of osteophytes, joint space width, and subchondral bone sclerosis form the basis of assessment. Literature reports that half of people afflicted with knee pain that are at or above age 55 show no definitive plain film osteoarthritis. (1)

9. In middle-aged women, significant association was shown between radiographic knee OA severity and pain and MRI findings of cartilage defect, meniscal tear, osteophytes, subchondral cysts, sclerosis, joint effusion, and synovitis. (6)

10. Wenham and Conaghan conclude that MRI in osteoarthritis has improved the disease’s phenotyping and our understanding of the anatomic regions involved, but it is still uncertain when osteoarthritis truly begins. The authors ask whether OA should be diagnosed when subchondral bone or cartilage abnormality occurs or when symptoms start. Since abnormalities of synovium and subchondral bone both have highly innervated morphologies, these appear to be pathologic areas most associated with knee pain. They could represent targets for new treatments aimed at symptomatic relief. (1)

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**What experimental treatments have been or are being considered?**

1. Novel therapeutic approaches for late-stage osteoarthritis may include stem cell therapy for cartilage regeneration. Repair tissue from human articular cartilage in late-stage osteoarthritis contains a unique progenitor cell population called chondrogenic progenitor cells, which show stem cell properties and high chondrogenic potential. (7)

2. Work is ongoing to assess the molecular aspects of cartilage lubrication, attempting to decrease friction experienced by cartilage. (8)

3. Licofelone, an NSAID, demonstrated decreased joint damage in animal models with osteoarthritis, with MRI demonstrating prevention of cartilage volume loss. (9, 10)

4. Human cartilage has been shown to contain a high number of cells with progenitor cell markers, and recently, these markers have been shown to change in distribution in OA-affected articular cartilage. (11)

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5. Review of osteoarthritis clinical trial literature reports that a multitude of new targets directed at neuronal transduction/excitability, conduction, sensitization, and transmission have come to the fore, with multiple compounds coming into development. Creation of pharmaceuticals to modify OA symptoms is proceeding along the plethora of pain pathways, with multiple agents in advanced stages of clinical development. Le Graverand-Gastineau discusses the pronounced importance of understanding the composite of tissues at play in osteoarthritis pathophysiology, noting that currently much is still unknown outside the purview of hyaline articular cartilage. (12)

6. The heterogeneity of structural change in osteoarthritis confounds the search for disease-modifying pharmaceutical agents. In this light, a recent review of the progress made toward identifying structure-modifying drugs was reported in an issue of 2009 Medical Clinics of North America. (13) The authors note that since cartilage has been the focus of attention in osteoarthritis, chondroprotective agents were termed disease-modifying osteoarthritis drugs. The authors report that “varying levels of evidence suggest that glucosamine sulphate, chondroitin sulphate, sodium hyaluronan, doxycycline, matrix metalloprotease (MMP) inhibitors, bisphosphonates, calcitonin, diacerein, and avocado-soybean unsaponifiables can modify disease progression.” (14) The authors note that the following agents are being studied:

   A. Small molecule inhibitors of MMPs – Several of these candidates are specific for MMP-13, which the authors note is overexpressed by OA cartilage.

   B. Tetracyclines have been shown to decrease severity of OA in animals, probably by inhibiting MMP activity.

   C. Diacerein has shown slowing of radiographic progression of hip OA.

   D. Bisphosphonates are hypothesized to perhaps be of use because of the strong increase in bone remodeling with OA, but have shown clinically disappointing results.

   E. Calcitonin

   F. Glucosamine and Hyaluronans

   G. Avocado-soybean unsaponifiables, reported to repress chondrocyte catabolic activities and increase accumulation of proteoglycan by OA chondrocytes in culture.

   H. Other targets being explored include synovitis. Investigations in this regard have included intraarticular injection of a specific bradykinin-B2 receptor antagonist, which reduced OA knee pain more potently than placebo injection.

   I. Nerve growth factor (NGF) has been a target of interest since NGF and its receptors find expression in synovial, meniscal, and articular cartilage tissues. A humanized monoclonal antibody against NGF (RN624 Tanezumab) has undergone study in patients with chronic OA pain, showing improvement in WOMAC scores compared to placebo.

   J. Other investigations are studying the potential structure-modifying role of vitamin D and the bone morphogenetic protein family of protein-signaling molecules. Another potential target for therapy in OA may relate to the increased vascularization found in areas of OA bone remodeling.

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K. Other potential agents include cathepsin K and aggrecanase inhibitors. As cathepsin K may be upregulated in OA cartilage and inflamed synovial tissue, it can degrade native collagen and aggrecan that provide compressive resistance to tissue.

7. Prostaglandin E2 has been shown to exert anti-anabolic effect on human articular cartilage in vitro and therefore receptor antagonists may provide effective therapeutic agents for OA treatment. (15)

8. Undenatured type 2 collagen has been reported as showing effective treatment in osteoarthritis in preliminary human and animal trials. Studies showed improvements in the Western Ontario Mc Masters Osteoarthritis Index (WOMAC) Score. (16)

9. Oral salmon calcitonin given twice daily resulted in decreased markers of bone resorption and cartilage degradation. (17)

Where are we in the development of artificial cartilage or menisci?

1. Synthetic gels that are tough and resilient have proved a problem in the knee due to compressive forces causing the material to protrude sideways. A goal has therefore been to coax cartilage cell growth on synthetic templates in hopes of providing resilience. Advances in the development of artificial cartilage include progress in the creation of three-dimensional high-strength scaffolds which are then seeded with cartilage-producing chondrocytes. (18)

2. Tissue engineering using biocompatible scaffolds which incorporated specific cell sources and bioactive molecules was reported as showing promise for cartilage tissue repair. (19)

Conclusion: Structural knee OA changes depicted by MRI can serve as a biomarker for the disease and may occur without symptoms. A variety of therapies plugging into a multivariable equation will likely always be required to combat this disease. Experimental therapies include agents targeted at stem cells for cartilage regeneration; neuronal transduction/excitability, conduction, sensitization, and transmission; chondroprotective agents; and artificial cartilage and menisci.

Sources


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12. Le Graverand-Gastineau HMP. "OA clinical trials: Current targets and trials for OA. Choosing molecular targets: What have we learned and where are we headed." Osteoarthritis Cartilage. 2009 Apr 22 (Epub ahead of print).


