

In Search of a Better, Cheaper Test

For someone with osteoarthritis (OA) of the knee, every step can be agony. Going down a flight of stairs, the bones of the knee joint can actually be heard protesting, with creaking, crackling sounds, the loss of their slick cushion

of articular cartilage. Each effort to flex the stiffened joint produces a stabbing pain. A patient with these symptoms is typically sent for standing knee X-rays to determine the extent of cartilage degeneration, seen by a narrowing of the joint space between the tibia and femur. The space can become so narrowed that bone literally grinds against bone, making the knee even more inflexible and painful.

Degeneration of cartilage is usually attributed to wear and tear; indeed, more than 80 percent of people over age 50 have some evidence of OA on X-rays. But some people who report excruciating pain do not always show extensive cartilage loss. That's because there's more to OA than meets the eye on X-rays, says Steven B. Abramson, M.D., Chairman of the Division of Rheumatology at NYU Hospital for Joint Diseases and Vice Dean for Education, Faculty, and Academic Affairs. High-resolution magnetic resonance imaging (MRI) often reveals disease involving the entire knee joint.

"In osteoarthritis, there's a lot of disease in the soft tissues surrounding the cartilage that can't be seen on an X-ray," says Dr. Abramson. "When you do an MRI, you see disease in more than 50 to 60 percent of people being examined—disease in the bone, the synovial tissue, the meniscus, and the ligaments. That probably accounts for a majority of cases where the patient experiences pain, but where routine X-rays don't show major joint space narrowing."

Signs of inflammation seen on high-resolution MRI include fluid accumulation

in the joint lining (synovium), thickening and proliferation of synovial tissue much like that of rheumatoid arthritis (RA), and lesions that have been termed bone marrow edema but are actually fluid filled with inflammatory cells. A number of recent studies have linked these bone lesions to increased pain and disease progression in OA.



The mainstay of treatment for OA pain is nonsteroidal anti-inflammatory drugs (NSAIDs). While cartilage contains no pain fibers, they are present in soft tissue and bone. NSAIDs are likely reducing pain in part by dampening inflammation in these other structures, says Dr. Abramson, who pioneered research into inflammation in OA.

In the mid-1990s Dr. Abramson's lab discovered that nitric oxide, a major mediator of inflammation, was produced by OA cartilage. Since then, his team has been among the leaders investigating the idea that inflammation is actually central to the development and progression of OA. They have found that the joint is damaged both by cellular fragments of degrading cartilage and by inflammatory chemicals, or cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF). Both of these pass into the bloodstream, acting as potential biomarkers of OA. Dr. Abramson's group has just launched a major study to track OA progression, comparing these biomarkers and MR images.

The OA Study, one of five funded by the National Institutes of Health as part of the OA Biomarkers Network, will be based at the Seligman Center for Advanced Therapeutics at NYUHJD. An invaluable resource for patients and researchers alike, the Seligman Center is a 3,300-square-foot state-of-the-art translational research center established to facilitate clinical research in arthritis and systemic lupus erythematosus. As part of the study, 150 patients with OA of the knee at NYUHJD will be followed for two years. Questionnaires will be used to quantify pain and blood tests every six months and will look for blood biomarkers of OA. The biomarkers and questionnaires will then be correlated with high-resolution MR images of the affected knee to track disease progression. A major focus of the study will be to assess the predictive value of gene expression by circulating white blood cells as markers of disease progression in OA.

"We hope to determine how good the specialized blood tests, so-called biomarkers, are at reflecting joint abnormalities revealed by MRI and whether such blood tests predict which patients will get worse," explains Dr. Abramson. "If you can do a blood test instead of an MRI, it would be much more cost-effective and could help to individualize treatment. You could potentially follow a patient and, based on an inexpensive blood test, say, 'I think at this point you need drug X.'" It's also hoped that the study will provide more information on how OA develops and progresses, with biomarkers offering potential targets for disease-modifying drugs. ●