findings are highly relevant to the associations that have been observed between negative expectations of pain-related outcomes and the relatively low preferences for TKA among African Americans[10,11]. We also believe it is reasonable to use research concerning medical decision-making, such as tests of prospect theory, to develop interventions that may alter the patient's pain-related beliefs and thus help reduce ethnic disparities in preference for TKA or other health care interventions. However, as we begin to test our theory-based interventions, it will be imperative that we continue to perform both quantitative and qualitative studies of patients from diverse backgrounds so as to better understand their needs, beliefs, and experiences with health care[12]. This understanding will be essential to the development of optimal psychosocial or educational interventions to reduce ethnic disparities in health care preferences and evaluate the effects of these interventions.

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FINDING CLINICAL ENDPOINTS AND BIOSURROGATES IN PRECLINICAL KNEE OSTEOARTHRITIS

Paola De Pablo and Matthew H. Liang

To evaluate disease-modifying drugs for OA (DMOAD) among subjects who have no or minimal symptoms, but who are destined to develop OA or to attempt primary prevention in those with early signs of OA on radiographs and/or MRI, we will need to develop and validate surrogate outcome measures for preclinical disease[1].

Outcome variables currently used in clinical trials assessing DMOAD have focused on pain, function, patient global assessment, and structural changes[2]. Subjective measures are limited in their ability to detect change and are prone to floor and ceiling effects. In contrast, outcomes such as rate and extent of cartilage damage, change in joint space width (JSW) on radiographs, and cartilage volume on MRI have face validity, provide objective measurements, and are continuous variables. The incidence and extent of cartilage surface defects by arthroscopy or MRI also have face validity, permit objective measurement, and are continuous variables, but their significance with respect to disease progression in asymptomatic subjects or patients with early OA remains to be established.

Surrogate endpoints. Useful clinical endpoints are outcomes that measure meaningful clinical outcomes (i.e., need for total joint arthroplasty, or mortality) or how a patient feels or functions. Surrogate endpoints substitute for a true endpoint and are often not perceived or felt by the patient. Examples include measures of cartilage degradation, such as urinary C-telopeptide fragments of type II collagen (CTX-II), which has been associated with both prevalence and progression of radiographic OA and JSW. For a surrogate endpoint to be an effective substitute for the clinical outcome, effects of the intervention on the surrogate must reliably predict the overall effect on the clinical outcome[3]. Surrogate endpoints should be of proven reliability, validity, and sensitivity to change. Hence, if a surrogate outcome measure is to be used to evaluate a chondroprotective agent, it must predict cartilage loss.

How might surrogate endpoints for preclinical OA be identified? Let us speculate on one possible study: For this, we would assemble a group of subjects at very high risk of

developing knee OA (KOA). A wide range of risk factors has been identified. These include age, sex, race, obesity, periarticular muscle weakness, malalignment, nerve injury, proprioceptive defects, repetitive joint stress, and knee injury. For secondary OA, risk factors include crystalline disease (urate or calcium pyrophosphate dihydrate) and inflammatory arthritides; metabolic disorders, such as hemochromatosis, ochronosis and acromegaly; inherited collagen mutations; and congenital hip dysplasia. In addition, low dietary intake of vitamin C and low dietary intake and low serum levels of vitamin D have been associated with radiographic progression of knee OA. As well, young women with a history of severe anterior cruciate ligament (ACL) injury, or subjects with meniscal tears and meniscectomy, are particularly prone to accelerated KOA within 12 or so years and would be an ideal population for this study[4].

This population could be enriched for developing OA by genotyping. Several chromosomal regions have genetic linkage with OA. Chromosomes 1, 2, 4, 7, 15, 16, and 20 are likely to encode susceptibility genes[5,6]. Polymorphisms of genes for type II collagen (COL2A1), type I collagen (COL1A1), aggrecan, insulin growth factor-1, transforming growth factor-ß, estrogen receptor-α, vitamin D receptor polymorphisms, and multiple single nucleotide polymorphisms from candidate genes in OA have been associated with disease susceptibility and progression.

In this hypothetical study, baseline assessment and followup evaluations would include a detailed questionnaire on symptoms and functional impairment. The symptom inventory would include questions about presence and severity of mechanical symptoms, the location and duration of symptoms, and changes in type of symptoms or intensity. The most widely used outcome measure in OA studies is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[7]. However, the Knee injury and Osteoarthritis Outcome Score (KOOS)[8], designed for knee injury, captures a wider range of impairments and functional limitations seen in younger and more functional individuals. The KOOS consists of 5 subscales: pain, other symptoms, function in daily living, function in sport and recreation, and knee-related quality of life, as well as the entire WOMAC.

In asymptomatic subjects, it may be possible to measure subtle impairment, by a performance-based test that challenges and stresses the limits of the individual, that could be related to objective JSW in KOA. In rating function, there is likely to be a threshold in the individual's perception of where it becomes "symptomatic," when their performance does not meet expectations or allow them to do what they have to do. Patient-oriented measures are usually more sensitive and responsive and relevant in advanced KOA[2]. A standardized test designed to provoke symptoms or set the functional limits of the subject with preclinical KOA — analogous to the exercise treadmill test to detect subclinical ischemic heart disease — would be applied.

Imaging studies. Change in JSW on serial knee radiographs is a surrogate for articular cartilage loss and is considered the best method for evaluating disease progression in knee OA[9,10]. It is limited by joint positioning, which dramatically affects measurement of the JSW[11,12], by its inability to visualize articular cartilage directly, and by its lack of correlation with articular symptoms and function. MRI offers a more sensitive and accurate test than radiography for detecting morphologic changes in articular cartilage, such as swelling, surface fraying, fissuring, thinning, and full-thickness cartilage loss. Bone marrow edema has been associated with subsequent progression of cartilage loss. MRI images correlate with arthroscopic grading scores. MRI-determined reduction in cartilage volume and the extent of focal and generalized cartilage loss and of subchondral cysts and sclerosis are associated with poorer outcome. MRI can detect interval cartilage loss over a short period (< 2 yrs). In patients with moderately symptomatic KOA, knee cartilage volume loss occurs as soon as at 6 months' followup. In subjects with OA, tibial cartilage volume is lost at a rate of 5% per year, although it may be more rapid early in the disease, when more cartilage is present. The main factor affecting cartilage loss is initial cartilage volume. MRI can measure progression of knee OA and help identify patients with rapidly progressing disease. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is a noninvasive technique to study cartilage glycosaminoglycan (GAG) content *in vivo*. A recent study evaluating dGEMRIC in patients with preradiographic degenerative cartilage changes (early KOA) found that dGEMRIC can identify GAG loss in early stage cartilage disease[13]. MRI enhancement with gadolinium has the promise of being a sensitive and responsive endpoint in KOA.

In our example (Figure 8) these variables would be assessed at baseline and at regular followup points. In time, after a number of patients developed manifest KOA, it would be possible to examine all potential surrogate endpoints assessed over the course of study and the extent to which they correlate with cartilage loss.

In summary, preventing or delaying disease progression in OA is *the* challenge for the field. To accomplish this we will first need to identify subjects at high risk for OA, using the best epidemiologic data possible. Then, we will need to perform studies to identify the earliest symptoms and functional problems of subjects with early OA (this, surprisingly, has never been done!) and identify potential surrogate endpoints for the evaluation of treatment response in the subclinical phases of the disease. Documentation of preclinical structural joint damage with imaging studies, such as gadolinium-enhanced MRI, could provide a surrogate endpoint in asymptomatic, minimally symptomatic, or very early OA. The use of surrogate endpoints to measure cartilage damage should reduce the sample size needed for clinical trials evaluating DMOAD and improve patient retention by reducing the duration of clinical trials and overall costs.

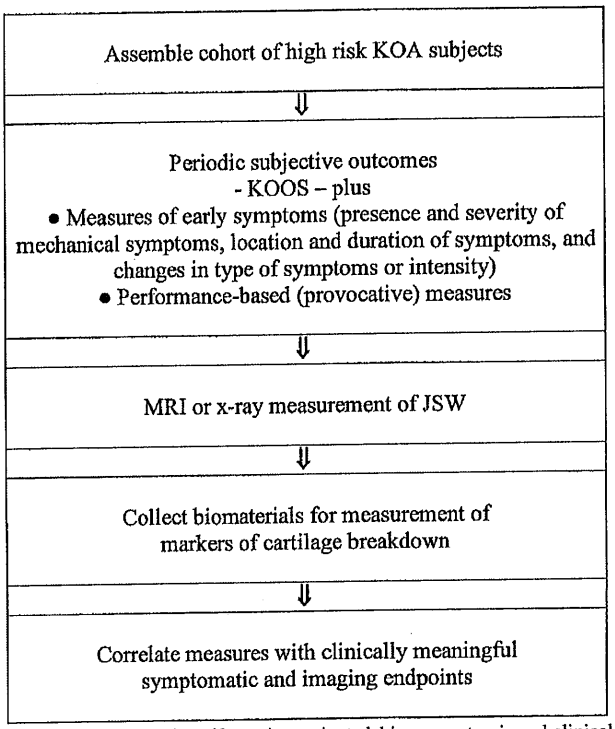

Figure 8. Study to identify patient-oriented biosurrogates in subclinical knee OA (KOA).

Although many risk factors for KOA have been suggested, young women with severe knee injuries represent a group who develop accelerated OA. With their numbers increasing, such subjects could be studied efficiently to identify clinical endpoints and biomarkers. The US National Institutes of Health OA Initiative has a goal of validating biomarkers, but it targets a much older population (45–79 yrs) in which disease has already been established and rate of OA progression is slower, thus prolonging the time to discovery.

However, whatever endpoint is to serve as an effective substitute for the clinical outcome, the effects of the intervention on the surrogate must reliably predict the overall effect on clinical outcome. Therefore, necessarily the endpoint should be related to meaningful, patient-oriented outcomes.

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WHY CHOOSE HIP OSTEOARTHRITIS AS A HUMAN MODEL FOR EVALUATION OF DRUGS IN OSTEOARTHRITIS?

Maxime Dougados

Background

Most of the current treatments for OA are aimed at relief of symptoms, but there is modest evidence that at least some treatments can also retard breakdown of articular cartilage, as evaluated by radiography or arthroscopy. A naïve and simple classification of drugs has been proposed to distinguish drugs that relieve symptoms but have no effect on structure from those that interfere with cartilage breakdown without necessarily relieving symptoms.

Although OA can affect any joint in the body, it mainly affects 4 sites: the spine, hand, hip, and knee. Because of the complexity of structural evaluation of both spine and hand OA, trials of disease-modifying OA drugs are usually conducted in patients with either hip OA or knee OA. Despite tremendous improvement in the conduct of clinical trials in hand OA, the pilot and pivotal studies evaluating so-called symptomatic drugs similarly remain focused on either hip or knee OA.

The question that eventually confronts those designing an OA clinical trial relates to the choice between hip and knee. This choice can be based on several considerations: