Editorial

The Use of Biochemical Markers of Bone and Cartilage Metabolism to Monitor Osteoarthritis — Dreams and Reality

In this issue of *The Journal*, Bruyere, *et al.* attempt to validate the use of biochemical markers to predict osteoarthritis (OA) progression, and show that if one compares large groups of individuals this can be achieved with some success for some markers. This adds to the considerable effort that has been expended for the past decade toward evaluating whether markers of bone and cartilage metabolism can be of value to the rheumatologist, and the utility of such markers have both their proponents and opponents. It is perhaps time to take a step back and consider: Why does the rheumatologist need marker analysis? What are the potential values and limitations of currently used markers? and What characteristics should the ideal marker possess?

Clinical rheumatologists dream of a marker that can be used in individual patients to verify the presence of disease early, prior to overt joint damage; to provide an indication of any change in disease status on followup; to identify those at risk for relatively rapid progression of their disease; and to assess the efficacy of antiinflammatory and chondroprotective drug therapy at retarding disease progression and possibly initiating repair.

The interest in biochemical markers arose because of their potential to fill these needs in a reliable, rapid, and cost-efficient manner. The ultimate value of any marker lies in it being a specific indicator of matrix degradation or synthesis in one of the joint tissues, thus making data interpretation uncomplicated. Unfortunately, the utility of many markers used in the assessment of OA is fraught with potential problems, as the metabolic relevance of the marker and its tissue of origin are often in question. Further, the ideal marker should be amenable to analysis in serum or urine, but the lack of sensitivity of some assays and the focal nature of the OA in some patients may limit the usefulness of marker analysis to the synovial fluid (SF) from the affected joint. This can be technically difficult in the absence of overt effusion, and of ethical concern for repeated sampling. An ideal marker should also be present at low and constant concentrations in the normal individual, so that any increase in concentration is unambiguous during clinical followup.

For marker analysis to be reliable in any body fluid it is necessary to assume that marker concentration is a reflection of only the metabolic status of the joint tissues, and that it is independent of variation in SF volume and rate of clearance via the synovium, liver, and kidneys, etc. Unfortunately, such variability does exist and contributes to the wide range of individual variation that is characteristic of patient analysis. Even if one is willing to ignore such variation, it is necessary to be sure that one knows the tissue of origin of the marker and whether its presence is indicative of synthesis or degradation. This is not always the case with markers of cartilage metabolism, yet these markers are often favored in OA research due to the intimate relationship between the disease process and articular cartilage degeneration. However, one must not forget that OA exhibits both reparative and degenerative features and therefore marker release into the SF may be of either catabolic or anabolic origin. As the degree of matrix synthesis and degradation varies with disease progression, all markers are not of equal value throughout the disease.

A multitude of markers of cartilage metabolism have been studied, including those related to extracellular matrix proteins and the proteinases and inhibitors involved in controlling their degradation. Type II collagen and aggrecan have received particular attention because of their high abundance in the extracellular matrix of articular cartilage. However, if one is undertaking analysis of these markers in serum or urine, one must remember that both macromolecules are also present in the intervertebral disc and that disc degeneration is a feature of normal adult life.

*See* Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee OA, *page 1043*
Markers of collagen metabolism include cross-link and propeptide release, which are potentially reliable indicators of collagen degradation and synthesis, respectively. Markers of aggrecan metabolism include chondroitin sulfate and keratan sulfate epitopes and core protein fragments, although interpretation of marker significance is less clear. The chondroitin sulfate epitopes of common interest (846 and 3B3-) are not present on the aggrecan of normal adult cartilage, but are present on the aggrecan of young juvenile cartilage and reappear on the newly synthesized aggrecan of the osteoarthritic joint. As such they are taken as being indicative of aggrecan synthesis. However, it is not clear whether all aggrecan synthesis in the adult need involve these epitopes. The keratan sulfate epitopes of common interest (5D4 and AN9P1) represent oversulfated regions on the aggrecan of adult cartilage, and their release is therefore taken as being indicative of aggrecan degradation. However, the epitopes may also be present on newly synthesized aggrecan. A similar problem exists with aggrecan core protein fragments, which could be released due to the degradation of resident or newly synthesized molecules.

Several other cartilage matrix proteins have received attention, initially because of their proposed cartilage specificity. The most studied is the cartilage oligomeric matrix protein (COMP), which is present in cartilage of all ages. Its release is usually taken to be indicative of matrix degradation, although it could indicate elevated synthesis and lack of retention by the degenerative matrix. Interpretation of COMP analysis is complicated by its synthesis in noncartilaginous tissues, particularly the synovium. A protein termed gp39 (YKL-40) has also been studied. This protein is not made by normal chondrocytes, but is a product of chondrocytes in the arthritic joint and therefore reflects new synthesis. However, it can also be a product of synovial cells. Matrix metalloproteinases (MMP) and their tissue inhibitors (TIMP) have also received attention. The MMP include several collagenses, gelatinases, and aggrecan-degrading enzymes, and elevation in their synthesis or depletion in TIMP synthesis has been taken as indicative of increased matrix degradation. However, MMP and TIMP synthesis is a feature of all connective tissues, and elevated MMP synthesis need not result in increased degradation, as synthesis is as a latent proenzyme and is independent of subsequent activation.

Metabolic markers of bone and synovium have also been used to assess OA. Of the bone markers, serum osteocalcin as a monitor of new bone formation and urinary type I collagen cross-links as a monitor of bone resorption have been particularly favored. The usefulness of these markers may be limited in an elderly patient with OA who presents with altered bone metabolism due to osteoporosis. Serum bone sialoprotein concentration may present a means of focusing on the osteoarthritic event, as this bone marker is concentrated at the osteochondral interface where metabolic changes are occurring in the osteoarthritic joint. Serum hyaluronic acid has been used as a monitor of OA, although it is really a reflection of perturbation to the synovium. As with many serum markers that are released via the SF, sampling time is critical as there can be a large variation in SF content and release with the absence or presence of joint motion.

Even if one professes an understanding of the significance of any metabolic marker, there is the issue of how one evaluates its validity as a monitor of osteoarthritic status. This is commonly performed by comparison using radiography as the gold standard. However, there is an inherent incompatibility between marker analysis and radiographs, as the former technique monitors the metabolic status of a joint tissue at a given point in time, whereas radiography monitors cumulative changes that have occurred during the whole time that the joint has been osteoarthritic. There is no a priori reason why the degree of cumulative change should correlate with metabolic events on any given day in a disorder such as OA, where in humans the mechanism of initiation and the course of progression can be very variable. Correlation between radiographic parameters such as joint space width and metabolic markers of articular cartilage metabolism may be more likely in animal models of OA, where disease onset and progression are relatively uniform, but even then correlation need not be continuous, as the contribution from anabolic and catabolic events varies throughout the course of the disease. Similar considerations apply to other imaging techniques, such as magnetic resonance imaging, that while providing greater resolution of joint pathology than radiography are still measures of cumulative change.

At the present time markers have proved useful for establishing metabolic differences between cohorts of patients who can be distinguished by the clinical presentation of their disease. The large variation and overlap observed in such analysis, however, has tended to limit the value of markers for application to individual patients, which is the major clinical need. This raises the question of whether marker use will remain a dream or become a reality in clinical practice in the near future. Certainly, markers are needed, as they have the potential to provide information on changes in tissue metabolism occurring over a short time period, which is essential for monitoring disease progression and drug therapy in a longitudinal manner. However, it is likely that a battery of markers reflecting abnormal synthesis and degradation of various macromolecules in cartilage, bone, and synovium will be needed to obtain a clear picture of what is happening in the joint with respect to pathological changes. It is also essential to use markers where the presence and consequence of a change in concentration is unambiguous if one is to know whether there is exacerbation or remission of the disease process and
whether a particular therapy is beneficial or detrimental. The need for and potential of biochemical markers in rheumatology is great, but at present we need to reevaluate how marker technology can be best applied and developed to meet the needs of the rheumatologist.

PETER J. ROUGHLEY, PhD, Genetics Unit; SHERIF EL-MAADAWY, MB, BCH, Joint Diseases Laboratory, Shriners Hospital for Children, 1529 Cedar Avenue, Montreal, Quebec, Canada H3G 1A6

Address reprint requests to Dr. Roughley.

REFERENCES