Biochemical Markers for Osteoarthritis: From the Present to the Future and Back to the Past

Matrix molecules turning over in articular tissues, or their metabolic fragments, are expected to appear in the serum or urine where they can be quantified, generally by ELISA or radioimmunoassay. These assays for “markers” of joint tissue turnover provide the possibility of sensitive correlations with clinical and radiological assessment of joint damage. This possibility is intuitively attractive to the pharmaceutical industry for drug development, since alterations in the levels of biochemical markers in serum or urine may, in theory, precede slowly developing radiological and clinical change.

However, it is well recognized that the measurement of joint tissue molecules or fragments in the serum or urine reflect complex metabolism in a multicompartment model, which can also be affected by the phasic nature of OA. One approach is to use “clusters” of markers, chosen more or less for their presumed biochemical function. In the interesting report by Patrick Garnero and collaborators in this issue of *The Journal*, 10 molecular markers of bone, cartilage, and synovium have been used and correlated with disease activity and radiological joint damage. The cohort, gathered from 26 rheumatology departments in France, consisted of 376 patients taken from a larger group of patients with hip OA that participated in a clinical trial on diacerein (ECHODIAH). The biochemical measurements were done at baseline, i.e., before the test drug was administered. Using principal component analyses, the investigators found that the different markers could be segregated into 5 different clusters, which, they speculate, may reflect different pathophysiological processes of OA, namely bone turnover, cartilage degradation, or synovitis.

Among the markers analyzed, urinary CTX II demonstrated the most consistent association with both joint pain [C-reactive protein (CRP) elevation was also associated with pain] and the width of the radiological joint space. In another recent study it was found that knee OA, spine disc degeneration, and hand OA contributed significantly and independently to increased urinary CTX II levels in postmenopausal women. Also, an interesting association noted by Garnero, et al relates to serum YKL-40 (cartilage GP-39). This glycoprotein was considered to be closely tied to cartilage differentiation and chondrocyte and synoviocyte proliferation, but was found to segregate together with serum CRP, suggesting that YKL-40 may also be an inflammatory marker. The authors correctly point out that because of the cross-sectional design of their study, they cannot use their data for prediction of joint damage. However, in a recent large epidemiological study it was found also that urinary CTX II was associated with both prevalence and progression of radiographic OA at the knee and hip, and the association seemed stronger in subjects with joint pain. The correlation between CTX II and symptoms is interesting, but it would be perverse to suggest (and the authors do not) that a biochemical marker should be used to determine who has symptoms.

Almost certainly, the ECHODIAH cohort is heavily biased in favor of patients with significant symptoms. But obtaining low selection bias “control” populations is a non-trivial matter, with many issues to consider. Among large epidemiological studies with low selection bias is the Canadian Multicenter Osteoporosis Study (CaMOS), whose sampling frame consists of all residential telephone numbers in predetermined geographical study centers, from which roughly 10,000 subjects have been randomly selected. Now in its seventh year, CaMOS has provided “normative” data for quality of life and stability over time. Extending the concept of “normative” data to biochemical markers has a number of problems, including how to handle asymptomatic subjects with radiological OA. However, a population with low selection bias, studied longitudinally for a long time, would be needed to give us a clearer insight into the biological significance of biochemical markers.

So, from the present state of the art, what does the future hold for biochemical markers in body fluids? If one takes the point of view that markers reflecting articular cartilage metabolism are central to the prognosis and treatment of OA, other cartilage-specific molecules, such as the cartilage specific (V+C) and hyperglycosylated forms of fibronectin, need to be explored. However, in terms of...
new technology the most promising application seems to be
the use of proteomics (the analysis of protein-expression pro-
files), utilizing gel and non-gel based mass spectrometry tech-
niques. Non-gel based techniques include SELDI-TOF-MS
(surface-enhanced laser desorption/ionization time-of-flight
mass spectrometry). Gel based approaches include 2-dimen-
sional gel electrophoresis coupled to MALDI-MS (matrix-
assisted laser desorption/ionization mass spectrometry)9.

The new proteomics technology has recently been used
to screen for patterns of putative biomarkers in the serum
that might be related to disease etiology, without a specific
candidate protein(s) or glycoprotein(s). Another application
is in the decision-making process with respect to treatment,
when there is believed to be heterogeneity of therapeutic
efficacy. The paradigm of prescribing celecoxib to patients
with familial adenomatous polyposis is instructive. Serum
proteomic profiles in these patients differ depending on
whether they are responsive or nonresponsive to celecoxib
(reduction in both the number and size of gastrointestinal
polyps)10. Thus, the technology could be used in risk-bene-
fit analysis with respect to an estimate of the cardiovascular
risk for this drug11.

But will advances in biomarker technology lead to better
insight in the pathogenesis and drug treatment of OA? Historically, human OA has been thought to be primarily
a remodeling process of bone, in the subchondral regions and
and at the margins of the joint, as had been comprehensively
described by Leon Sokoloff12 and previously by Lent
Johnson13. On the other hand, the Pond-Nuki dog model
(anterior cruciate ligament section) had provided a great
deal of impetus for experimentalists to regard OA primarily
as a disease of articular cartilage. Thus, it is hardly surpris-
ing that if a drug was originally developed around a bio-
chemical target located in either cartilage or bone, then the
endpoints and the markers in the clinical trials for that drug
would also be designed to reflect that target. Diacereine2,
which was initially developed as an interleukin 1 and colla-
genase inhibitor in articular cartilage, is an interesting case
in point, as there is now a significant literature indicating
that it may have effects on both cartilage and bone.

Further, even drugs that are thought to be bone-specific,
such as the diphosphonates, can be observed in experimental-
models to repair articular cartilage14. It is now apparent
that older pathological work on subchondral bone needs to
be revisited in view of the prominence recently given to sub-
chondral bone lesions, identified by magnetic resonance
imaging, that probably develop as a result of biomechani-
cally induced bone resorption15. A decreased prevalence of
these subchondral lesions in knee OA has been reported in
elderly women treated with alendronate and estrogen and a
reduction of symptoms in those treated with the diphospho-
late16. Thus, the siren song of newer technology for bio-
chemical markers must not seduce us from going back to
reevaluate the still poorly understood relationship of bone
remodeling to cartilage damage and, potentially, cartilage
repair, as well as the cause of symptoms.

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