Editorial

Biomarkers in osteoarthritis

Frances MK Williams and Tim D Spector

Twin Research and Genetic Epidemiology Unit, King's College London School of Medicine, St Thomas' Campus, London SE1 7EH, UK

Corresponding author: Frances MK Williams, frances.m.williams@kcl.ac.uk

Published: 16 January 2008
This article is online at http://arthritis-research.com/content/10/1/101

Arthritis Research & Therapy 2008, **10:**101 (doi:10.1186/ar2344)

See related research article by Hunter *et al*., http://arthritis-research.com/content/9/6/R108

Abstract

Biomarkers aid the study of osteoarthritis (OA) in a number of different ways. In this article we summarise briefly their multiple uses and reflect on how the study reported in a previous edition of *Arthritis Research & Therapy* should promote further investigation of cartilage oligomeric matrix protein (COMP). COMP is foremost among hitherto investigated biomarkers and is most consistently shown to predict knee OA progression. Precisely what role it plays in OA pathogenesis remains unclear and elucidating this may be key to defining, and then targeting, the cellular pathways involved in OA.

The field of osteoarthritis (OA) study is desperately in need of biomarkers. A sound biomarker could alter radically OA prediction, OA management, trials of therapies and our understanding of disease pathogenesis. Biomarkers are generally considered to be biological substances, although some workers view imaging and even traditional disease risk factors as biomarkers. In the present article, we shall consider only biological substances, which include proteins, RNA and DNA. Biomarkers may be used in isolation, in combination with each other or even in combination with imaging to provide more information about OA.

OA is a highly prevalent, age-related degenerative disease of synovial joints whose hallmark is cartilage loss. Although great strides have been made in the past decade to further the understanding of cartilage loss, subchondral bone abnormalities and the extra-articular inflammation of tendons and ligaments, there are still no disease-modifying agents for the treatment of OA. Current therapies are generally palliative, with analgesics, weight loss and muscle-strengthening exercises forming the bedrock of management before joint replacement is used. Generally, the favoured methods of OA assessment are imaging based, with plain radiographs widely used and magnetic resonance imaging (MRI), which remains relatively expensive, used much less. Plain films, however, relate poorly to patient symptoms, and abnormalities occur relatively late in disease. It is increasingly recognised that the very earliest pathological changes take place periarticularly, and are not captured well by plain film but are evident on MRI. A biomarker detectable very early in disease that could be measured in blood or urine would enhance our ability to detect early OA, would allow prognostication, and would be of great value to those conducting pharmaceutical trials of new agents. Such a biomarker would also help to shed light on the pathogenic mechanisms underlying the early stages of OA.

With this knowledge in mind, the Boston Osteoarthritis Knee Study group has looked at the relationship between MRI changes at the knee and a number of markers of cartilage turnover [1]. The group hypothesised that increased levels of cartilage degradation products and/or imbalance of cartilage synthesis and degradation markers would be predictive of subsequent cartilage loss.

Disappointingly, of the biomarkers studied only the baseline level of cartilage oligomeric matrix protein (COMP) was predictive of subsequent MRI-determined cartilage loss in the OA knee. For each unit increase in COMP, the authors report a sixfold increased odds of cartilage loss, even after adjustment for the known risk factors – age and body mass index [1]. COMP is a 435,000 Da pentameric member of the thrombospondin protein family. It was isolated initially from cartilage, is synthesised by chondrocytes and is present in small amounts in the synovium and tendon as well as being detectable in serum [2]. COMP is abundant in OA cartilage.

Previous studies have shown that serum COMP levels predict progression of disease in both subjects with radiographic knee OA at baseline [3] and those with knee pain and normal baseline knee X-ray [4]. The findings from the Boston Osteoarthritis Knee Study group complement what has been shown before [5]. COMP is going to be

COMP = cartilage oligomeric matrix protein; MRI = magnetic resonance imaging; OA = osteoarthritis.

helpful in selecting patients at high risk for cartilage loss for recruitment into clinical trials: more rapid assessment of the efficacy of a disease-modifying drug will be possible, and anything that helps facilitate clinical trials is a good thing. In addition, this finding and others may shed further light on the pathogenesis of OA. Serum COMP is known to be independently heritable [6], and further exploration of the genes controlling this may reveal new pathways in early OA pathogenesis, or indeed provide a better surrogate marker, as COMP levels are known to fluctuate nonlinearly over time [7]. Whether the elevated serum COMP levels are influenced by COMP released from ligaments and tendons – the very structures increasingly recognised as being involved in early disease [8] – will be an important question to answer.

Why did no other biomarkers, many of which were derived from collagen, show association? One problem in this area is that collagen products probably reflect activity in all tissues over the whole body (including other joints, bone and intervertebral disc), not just in the affected knee chosen for imaging. Add to this the wide day-to-day variation in many of the biomarkers measured, and picking up early changes in systemic levels of collagen-derived biomarkers seems unlikely. As the authors mention, it may be that the chosen specific endpoint of MRI cartilage loss was the problem here: perhaps bone marrow lesions would have had a stronger association. The most surprising finding occurs with collagen II crosslinking C-telopeptide, which has been shown to be associated in a number of previous studies mainly using X-ray data. These results may reflect the temporal nature of cartilage destruction in OA: using MRI, early cartilage damage is detected in which COMP and aggrecan are released. Collagen II degradation, as detected by collagen II crosslinking C-telopeptide, may come later.

Rather than dwell on disappointing collagen-derived markers, we should celebrate the positive. Evidence is accumulating that COMP predicts MRI cartilage loss and appears a useful biomarker of early OA. It will have many uses and, if more ammunition were needed, this paper should stimulate serious research into COMP's behaviour, shedding light on early pathogenic pathways, as well as determining its clinical usefulness as a biomarker.

Competing interests

The authors declare that they have no competing interests.

References

1. Hunter DJ, Li J, LaValley M, Bauer DC, Nevitt M, DeGroot J, Poole R, Eyre D, Guermazi A, Gale D, Felson DT: **Cartilage markers and their association with cartilage loss on magnetic resonance imaging in knee osteoarthritis: the Boston Osteoarthritis Knee Study.** *Arthritis Res Ther* 2007, **9**:R108.
2. Saxne T, Heinegard D: **Cartilage oligomeric matrix protein: a novel marker of cartilage turnover detectable in synovial fluid and blood.** *Br J Rheumatol* 1992, **31:**583-591.
3. Vilim V, Olejarova M, Machacek S, Gatterova J, Kraus VB, Pavelka K: **Serum levels of cartilage oligomeric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis.** *Osteoarthr Cartil* 2002, **10:**707-713.
4. Petersson IF, Boegard T, Svensson B, Heinegard D, Saxne T: **Changes in cartilage and bone metabolism identified by serum markers in early osteoarthritis of the knee joint.** *Br J Rheumatol* 1998, **37:**46-50.
5. Sharif M, Granell R, Johansen J, Clarke S, Elson C, Kirwan JR: **Serum cartilage oligomeric matrix protein and other biomarker profiles in tibiofemoral and patellofemoral osteoarthritis of the knee.** *Rheumatology (Oxford)* 2006, **45:** 522-526.
6. Williams FM, Andrew T, Saxne T, Heinegard D, Spector TD, MacGregor AJ: **The heritable determinants of cartilage oligomeric matrix protein.** *Arthritis Rheum* 2006, **54:**2147-2151.
7. Sharif M, Kirwan JR, Elson CJ, Granell R, Clarke S: **Suggestion of nonlinear or phasic progression of knee osteoarthritis based on measurements of serum cartilage oligomeric matrix protein levels over five years.** *Arthritis Rheum* 2004, **50:**2479-2488.
8. Tan AL, Grainger AJ, Tanner SF, Shelley DM, Pease C, Emery P, McGonagle D: **High-resolution magnetic resonance imaging for the assessment of hand osteoarthritis.** *Arthritis Rheum* 2005, **52:**2355-2365.