ulated by differential binding of repressor proteins to the promoter[12-14]. Numerous mutations in this gene have been described in association with pseudoachondroplasia and multiple epiphyseal dysplasia, conditions associated with precocious OA[12]. Mutant COMP does not undergo normal degradation or secretion and is retained, along with other matrix components, such as type IX collagen and aggrecan, within abnormally enlarged endoplasmic reticulum, resulting in impairment of chondrocyte function and enhanced apoptosis[12,15]. The relationship between these observations and clinical features of skeletal dysplasias can be conjectured, but the relationship to OA pathology remains elusive.

In summary, serum COMP has potential use as a biomarker of OA, but ethnic and gender differences must be considered in derivations of standards for this marker. Elevations in this marker have been associated with OA presence and severity and can predict OA progression. Certain therapies aimed at disease modification in OA and RA can influence serum COMP levels, which in turn reflect cartilage damage. Further clinical and longitudinal study of ethnic and other variation in serum COMP, and its association with OA load, symptoms, and functional status, will be important. This, in conjunction with basic research into the genetics of COMP regulation, its function, as well as mechanisms behind its association with OA, will be critical in determining where measurement of serum COMP fits in the complex array of potential biomarkers for epidemiologic studies, clinical trials, and ultimately, clinical application for treatment and prevention of OA.

REFERENCES

1. Mann HH, Ozbek S, Engel J, Paulsson M, Wagener R. Interactions between the cartilage oligomeric matrix protein and matrilins: Implications for matrix assembly and the pathogenesis of chondrodysplasias. J Biol Chem 2004;279:25294-8.
2. Johnson A, Smith R, Saxne T, Hickery M, Heinegard D. Fibronectin fragments cause release and degradation of collagen-binding molecules from equine explant cultures. Osteoarthritis Cartilage 2004;12:149-59.
3. Clark AG, Jordan JM, Vilim V, et al. Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. Arthritis Rheum 1999;42:2356-64.
4. Conrozier T, Saxne T, Fan CS, et al. Serum concentrations of cartilage oligomeric matrix protein and bone sialoprotein in hip osteoarthritis: a one year prospective study. Ann Rheum Dis 1998;57:527-32.
5. 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;50:2479-88.
6. Jordan JM, Luta G, Stabler T, et al. Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project. Arthritis Rheum 2003;48:675-81.
7. Bruyere O, Collette JH, Ethgen O, et al. Biochemical markers of bone and cartilage remodeling in prediction of longterm progression of knee osteoarthritis. J Rheumatol 2003;30:1043-50.
8. Dragomir AD, Jordan JM, Arab L, et al. Lower levels of serum cartilage oligomeric matrix protein in postmenopausal African-American and Caucasian women on current hormone replacement therapy [abstract]. Arthritis Rheum 2002;46 Suppl:S373.
9. Forsblad d'Elia H, Christgau S, Mattsson LA, et al. Hormone replacement therapy, calcium and vitamin D3 versus calcium and vitamin D3 alone decreases markers of cartilage and bone metabolism in rheumatoid arthritis: a randomized controlled trial. Arthritis Res Ther 2004;6:R457-R468.
10. Crnkic M, Mansson B, Larsson L, Geborek P, Heinegard D, Saxne T. Serum cartilage oligomeric matrix protein (COMP) decreases in rheumatoid arthritis patients treated with infliximab or etanercept. Arthritis Res Ther 2003;5:R181-R185.
11. Larsson E, Erlandsson Harris H, Larsson A, Mansson B, Saxne T, Klareskog L. Corticosteroid treatment of experimental arthritis retards cartilage destruction as determined by histology and serum COMP. Rheumatology Oxford 2004;43:428-34.
12. Posey KL, Hayes E, Haynes R, Hecht JT. Role of TSP-5/COMP in pseudoachondroplasia. Int J Biochem Cell Biol 2004;36:1005-12.
13. Issack PS, Liu Cj, Prazak L, Di Cesare PE. A silencer element in the cartilage oligomeric matrix protein gene regulates chondrocyte-specific expression. J Orthop Res 2004;22:751-8.
14. Liu CJ, Prazak L, Fajardo M, Yu S, Tyagi N, DiCesare PE. Leukemia/lymphoma-related factor, a POZ domain-containing transcriptional repressor, interacts with histone deacetylase-1 and inhibits cartilage oligomeric matrix protein gene expression and chondrogenesis. J Biol Chem 2004;279:47081-91.
15. Hecht JT, Makitie O, Hayes E, et al. Chondrocyte cell death and intracellular distribution of COMP and type IX collagen in the pseudoachondroplasia growth plate. J Orthop Res 2004; 22:759-67.

RELATIONSHIP BETWEEN SYMPTOMS AND STRUCTURAL CHANGE IN OSTEOARTHRITIS: WHAT ARE THE IMPORTANT TARGETS FOR THERAPY?

Paul A. Dieppe

What Is Osteoarthritis? OA can be defined as a condition of synovial joints characterized by focal areas of damage to, or loss of, articular cartilage, associated with new bone formation at the joint margins (osteophytes), changes in the subchondral bone, and variable degrees of mild synovitis and capsular thickening. This is a structural definition.

The pathology, if severe enough, is reflected by radiographic changes that include joint space narrowing (due to loss of volume of articular cartilage) and osteophyte formation. Epidemiological studies of OA rely on radiographic definitions and, therefore, on structural change. Such studies make it clear that the pathology we call OA is common, is associated with mechanical insults to joints, and is strongly age-related. It can occur in any synovial joint in the body but is common in only a few.

Musculoskeletal symptoms in older people. Regional musculoskeletal symptoms are common in older people — particularly chronic, use-related pain, gelling of the joints after inactivity, and a reduced range of joint movement. These are the symptoms we associate with OA.

There are no validated clinical diagnostic criteria for OA,

although the widely used American College of Rheumatology classification criteria emphasize age, morning stiffness of brief duration, joint pain related to activity, crepitus of the joint, and bony swelling[1]. These symptoms often localize to joints commonly affected by the structural changes of OA. This fact, along with the finding that severe symptoms can be relieved by surgically replacing a damaged joint, have fostered the belief that the structural changes cause the symptoms. This concept is consistent with the "medical model" of disease, which assumes that pathological changes lead directly to the clinical manifestations of a disease.

However, this medical (OA) model may not be a sufficient explanation for the high prevalence of chronic regional musculoskeletal pain in older people. Biopsychosocial models and their variants have been thought to be more appropriate than medical models for many other types of chronic pain, including fibromyalgia[2], and there is good evidence that psychosocial factors affect the symptoms described above[3]. Further, as argued below, it may be that the structural changes of OA are not a direct cause of pain.

The relationship between radiographic evidence of structural change and symptoms. Most studies of OA are based on the premise that structural changes cause symptoms. The starting points are either radiographic abnormalities (in community-based studies) or symptoms (in patient-based studies) and associations between the 2 are sought. However, critical analyses of the community-based data suggest that structural change, as defined by radiographic abnormality, is at best a weak risk factor for pain or disability. The first seminal observation in this field came from John Lawrence and colleagues[4], who carried out a population study in the North of England in which joint site-specific pain was related to presence of radiographic changes; the striking observation from this study was that many people with severe structural change were asymptomatic. Most subsequent observations have focused on the knee joint alone, rather than on other joints, as this is the most frequent site of pain and cause of disability associated with OA. At this joint site Lawrence's findings have stood the test of time.

The data led Hadler to write an article in 1992 with the title, "Knee Pain Is the Malady, Not Osteoarthritis"[5], in which he observed, "The epidemiology of osteoarthritis and the epidemiology of pain have little in common — not nothing in common, but surprisingly little." Hadler went on to outline the problem faced by doctors constrained by their medical model of disease with the observation: "What physician can see an osteophyte on an x-ray without inferring that it reflects the process that is causing the knee to hurt?". I agree with Hadler.

Problems arise when we try to squeeze an illness into a disease when the data do not support such an approach (Figure 5). I have little to add to Hadler's comments of 13 years ago, except to gloss them with some additional, more recent data. For example, in the late 1990s, Creamer, Hochberg, and colleagues published several articles about the determinants of pain in OA, based on analyses of data from the Baltimore Longitudinal Study of Aging[3]. They found, as have others, that psychosocial factors were important, and concluded that while structural joint damage predisposes to pain, the severity of the joint damage bears little relationship to the severity of the pain.

So, we must conclude that structural damage, as defined by radiographic changes consistent with pathology of OA, is only a weak risk factor for symptoms, and that the severity of the structural damage has little to do with the severity of symptoms. The data also show that psychosocial factors are important determinants of symptoms, suggesting that the biopsychosocial model is more appropriate than the medical model as a basis for exploration of this problem. However, we must add at least 3 caveats to this conclusion:

1. The conclusion is based on a surrogate marker of structural change, i.e., the radiograph. We know this to be an insensitive reflection of the degree of structural change. In addition, because it is poor at imaging soft tissues, radiography may not image those aspects of the pathology that are most important to the pain. Maybe MRI will do better.
2. Nearly all the data concern the knee joint. Similar studies have not been done with OA at other joint sites.
3. Most studies are cross-sectional, rather than longitudinal. It could be that OA is only a source of pain when the structure of the joint is changing.

What causes symptoms in OA? Pain is the dominant symptom of OA. But, as Lawrence showed, OA joint damage alone is not a sufficient cause of pain. Fifty years after

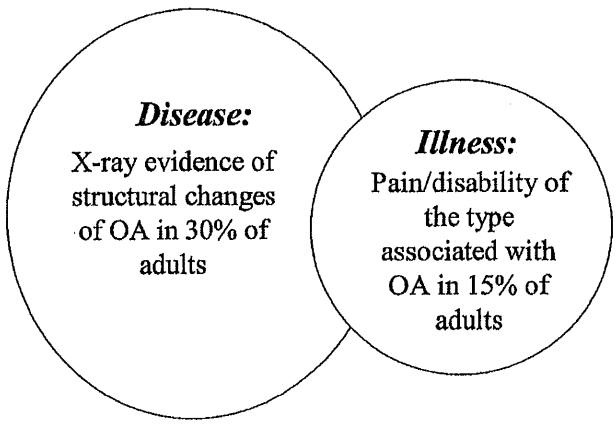

Figure 5. Structural changes of OA are common, as are the symptoms we associate with them. However, the 2 phenomena do not overlap fully. Structural changes are only one of a number of determinants of the illness of OA; others include psychosocial factors and comorbidity. We need to separate the disease from the illness, and stop assuming that the disease is the cause of the symptoms.

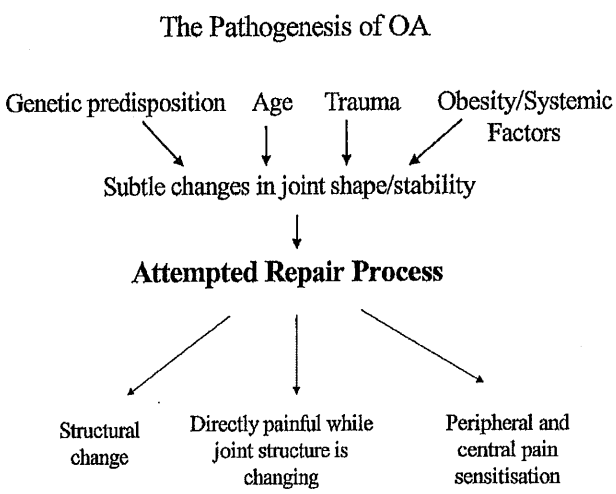

Figure 6. Likely pathways in the pathogenesis of both the structural changes and the symptoms of OA. Changes in joint shape and stability induce an attempt by the joint to repair damage. This is the "OA process." Pain is generated by direct nociceptive mechanisms when the process starts. In addition, in some people, peripheral and central pain sensitization occurs so that normal movements become painful. These are the people who develop chronic OA symptoms, which persist even if structural changes stabilize.

Lawrence, we still don't know why OA is sometimes painful[6]. Pain could arise from the synovium (inflammation), joint capsule (stretching), subchondral bone (raised intraosseous pressure), periosteum (elevation by osteophyte growth), or periarticular tissues (secondary to altered biomechanics of the joint). There are some data to support each of these hypotheses, but it is likely that in different individuals different types of tissue damage are important, perhaps, in part, explaining the heterogeneity of the clinical condition.

Recent data suggest that another important mechanism may be operating in patients with OA — sensitization of the nociceptive pathways, resulting in pain with normal movement of the joints[7]. If this is the case it may be that the OA process generates pain only initially, after which the joint/pain pathways are sensitized to pain in some patients, explaining the chronicity of the symptoms in some, but not all, of those with joint damage (Figure 6).

So, what are the important targets for t herapy? If we accept the primacy of some of the data summarized above, efforts to treat OA that focus on structural change alone are likely to be misplaced. The findings suggest we need to focus on other aspects as well, including:

- Biomechanical abnormalities that lead to joint damage
- Processes that initiate both joint damage and sensitization to pain
- Psychosocial factors that are determinants of symptom severity

In short, future management of OA should concentrate on the control of pain and on pain sensitization and disability in older people, without worrying about the type or severity of joint damage. That is not a new conclusion[8].

REFERENCES

1. Altman R. Criteria for the classification of osteoarthritis of the knee and hip. Scand J Rheumatol 1987;65 Suppl:31-9.
2. Hezemeijer I, Rasker J. Fibromyalgia and the therapeutic domain. Rheumatology Oxford 2003;42:507-15.
3. Creamer P, Lethbridge-Cejku M, Cost P, Tobin JD, Herbst JH, Hochberg MC. The relationship of anxiety and depression with self-reported knee pain in the community: data from the Baltimore Longitudinal Study of Aging. Arthritis Care Res 1999;12:3-7.
4. Lawrence JS, Bremner JM, Bier F. Osteo-arthrosis: prevalence in the population and relationships between symptoms and x-ray changes. Ann Rheum Dis 1966;25:1-24.
5. Hadler NM. Knee pain is the malady — not osteoarthritis. Ann Intern Med 1992;116:598-9.
6. Dieppe P. What is the relationship between pain and osteoarthritis? Rheumatology in Europe 1998;27:55-6.
7. Kidd BL, Photiou A, Inglis JL. The role of inflammatory mediators on nociception and pain in arthritis. In: Novartis Foundation Symposium 260 Osteoarthritic Joint Pain. Chichester: John Wiley; 2004:122-33.
8. Dieppe P, Brandt KD. What is important in treating osteoarthritis? Whom should we treat and how should we treat them? Rheum Dis Clin North Am 2003;29:687-716.

PAIN-RELATED BELIEFS AND AFFECTIVE PAIN RESPONSES: IMPLICATIONS FOR ETHNIC DISPARITIES IN PREFERENCES FOR JOINT ARTHROPLASTY

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In the 2002 Workshop[1] we described preliminary findings of our continuing work regarding central mechanisms involved in pain associated with knee OA. The major premise guiding our work is that our understanding of OA pain, and optimal management of this pain, requires that we attend to factors that influence the central processing of neurosensory input from affected joints and soft tissue as well as the factors that influence disease activity in the joint. We now describe recent findings concerning 2 factors relevant to the pain associated with knee OA: (a) pain-related beliefs and (b) ethnic variations in these beliefs, including expectations of the outcome of total knee arthroplasty (TKA). The latter discussion includes a description of a study we have recently initiated, involving methods for altering the negative pain-related beliefs that are associated with ethnic disparities in preferences for TKA.

Pain-Related Beliefs

Numerous investigations have shown that individual variations in pain-related beliefs are associated with differences in pain responses. This discussion focuses primarily on