PA metatarsophalangeal (MTP) view, fixed-flexion PA view, and the PA Lyon schuss view. Among these, 2 (the semiflexed AP and Lyon schuss) require fluoroscopy to position the knee. Only the semiflexed view employs an AP orientation of the x-ray beam. Although the latter protocol has been shown to represent a significant improvement over the standing extended AP view, its performance is affected by the need to correct for radiographic magnification. In contrast, the PA views of the knee in flexion do not require magnification correction and appear simpler and preferable to an AP view.

The position of the knee is identical in the Lyon schuss and fixed-flexion views. The major differences between these 2 radiographic protocols are in the use of fluoroscopy to adjust the angle of the x-ray beam to achieve optimal alignment of the medial tibial plateau in the former and the use of a Plexiglas frame to standardize knee flexion and foot positioning in the latter.

In the semiflexed MTP protocol, which does not use a positioning frame or fluoroscopy, knee flexion is less than in the fixed-flexion or Lyon schuss view by the length of the big toe. A head-to-head comparison of the 3 flexed PA views is currently lacking. However, reproducible alignment of the medial tibial plateau with the x-ray beam, as assessed by the intermargin distance (IMD) of the medial tibial plateau, is a major factor in the reliable measurement of changes in JSW in serial radiography and improves sensitivity to change[13]. In the Lyon schuss view, the optimal alignment of the medial tibial plateau that provides the greatest sensitivity to change in JSN requires an IMD < 1.2 mm[14]. While high performance of both the MTP and the fixed-flexion views has been reported, the reproducibility of alignment in serial MTP radiographs has been questioned[15]. In patients positioned with the Lyon schuss protocol, the quality of alignment is highly dependent upon use of fluoroscopy[16]. Reproducibility of the angle of knee flexion has been shown to be superior in the fixed flexion view to that in either the MTP view or semiflexed AP view. Thus, the data support the use of fluoroscopy for optimal alignment of the medial tibial plateau and of a Plexiglas frame to improve standardization of the angle of knee flexion.

Conclusion

Due to the great difficulty in obtaining high quality reproducible images of OA hips and knees, when the low average annual rate of JSN in the OA joint is taken into account the accuracy of JSW measurement in serial radiographs remains only marginal. For this reason, the duration of clinical trials of structure-modifying OA drugs remains lengthy. Further improvements in the acquisition of serial, high quality joint images should continue to improve the radiographic assessment of progression of hip and knee OA.

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UPDATE ON CARTILAGE OLIGOMERIC MATRIX PROTEIN AS A MARKER OF OSTEOARTHRITIS

Joanne M. Jordan

Cartilage oligomeric matrix protein (COMP), a 524 kDa

glycoprotein, is a member of the thrombospondin family of extracellular calcium-binding proteins. Originally described in cartilage, COMP is also found in ligaments, meniscus, tendons, synovium, and osteoblasts. COMP is composed of 5 identical subunits, with a carboxy-terminal globular domain that binds to collagens I, II, and IX; calcium-binding thrombospondin type 3 repeats; epidermal growth factor-like domains; and an amino-terminal coiled-coil domain. COMP may have a role in endochondral ossification and in stabilization of the extracellular matrix by its interaction with collagen fibrils and matrix components such as fibronectin and matrilins[1,2].

COMP has been thought of as a marker of cartilage catabolism. Serum levels of COMP are elevated in persons with OA and increase with an increasing OA burden, as measured by the severity of radiographic knee OA, its bilaterality, the concomitant presence of knee and hip OA, and the numbers of knees and hips with radiographic OA[3]. Elevation of serum COMP at baseline predicted progression of symptomatic hip OA[4], and rising levels of serum COMP have been predictive of progression of knee OA[5].

This update reviews selected pertinent literature about COMP published since 2002. First, clinical studies in radiographic and clinical OA will be described, followed by studies describing the influence of various therapies upon measurements of serum COMP. A brief description of recent advances in knowledge about the genetics controlling COMP production and function, and mechanisms whereby COMP may be associated with disease, will conclude.

Clinical Studies of COMP in OA.

We recently reported the first assessment of ethnic differences in serum COMP in the Johnston County Osteoarthritis Project, a population-based study of OA in African Americans and Caucasians[6]. In both ethnic groups, serum COMP increased with age and was higher in those with radiographic OA than in those without OA. African American women had significantly higher levels of COMP than Caucasian women; ethnic differences were not statistically significant in the men. Gender differences in serum COMP were also noted in Caucasians only, with men having higher levels than women. Importantly, the ethnic and gender differences in serum COMP could not be explained by differences in age, body mass index, height, presence or severity of radiographic OA, or number of other symptomatic joints[6].

Sharif and colleagues recently published a seminal study describing longitudinal variation in serum COMP and the effect of joint replacement on serum COMP[5]. In a study of 135 patients with primarily medial tibiofemoral radiographic OA, serum COMP was measured every 6 months for 4 to 5 years. Although there was overlap in serum levels between those whose OA progressed and those whose OA did not progress, mean serum COMP was higher in those whose OA progressed, defined as an increase in joint space narrowing of at least 2 mm or by reception of a total joint replacement. This was true at baseline and at each study visit.

Further, increasing COMP was associated with higher risk of progression. In 16 patients who underwent joint replacement during the study period, serum COMP rose after the surgery and remained elevated for up to 12 months. The authors speculated that this may have been due to increased release of COMP from other joint tissues, such as ligament and tendon in the replaced joint, or from increased production or degradation of COMP in the contralateral joint. They also concluded that the progression of OA is phasic rather than strictly linear[5].

Response of COMP to Various Therapies

If changes in a serum biomarker occur during therapy aimed at structure modification in OA, then that marker might be useful for monitoring therapy and/or shortening the duration of clinical trials of OA disease-modifying agents. Several clinical studies addressed this question with slightly different results. Bruyere, *et al* reported no association between baseline COMP and change in COMP with joint space width or scores on the Western Ontario and McMaster Universities Osteoarthritis Index in a study of glucosamine sulfate for OA[7]. In contrast, postmenopausal women receiving hormone replacement therapy (HRT) had lower serum COMP levels than those not receiving HRT[8]. This was noted also in a clinical trial of HRT in women with rheumatoid arthritis (RA), in which Forsblad d'Elia and others showed that serum COMP decreased with HRT over 2 years[9]. Crnkic and others examined serum COMP in patients with RA treated with tumor necrosis factor-α blockers infliximab or etanercept and found that serum COMP decreased at 3 months of therapy and remained low at 6 months in both responders and nonresponders by American College of Rheumatology 20% improvement criteria[10]. Finally, Larsson and colleagues demonstrated stable serum COMP levels in rats with collagen-induced arthritis treated with corticosteroid therapy, compared to increases in COMP over time in placebo-treated rats, with serum COMP highly correlated with degree of histologic cartilage destruction[11]. These studies show that certain therapies can influence serum COMP and that serum COMP reflects cartilage damage, suggesting that serum COMP might be useful as an early marker in clinical trials aimed at structure modification in OA.

Genetics of COMP Regulation

Although results of studies described above are intriguing, detailed knowledge of the functions of COMP remains incomplete. The gene encoding for COMP, which is located on chromosome 19p12-13.1., has been cloned. Tissue-specificity of COMP transcription may be negatively reg-

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.

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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,