Mechanically Induced Changes in COMP Concentrations Predict Changes in Cartilage Thickness after 5 Years

INTRODUCTION:
Knee osteoarthritis (OA) is a prevalent and debilitating disease, characterized by the degeneration of articular cartilage. Early detection and the ability to evaluate the rate of disease progression are important considerations in improving OA treatment. Serum derived biomarkers have been studied to evaluate OA disease state. However, the diagnostic performance of individual biochemical markers for predicting OA progression has been limited by large inter-subject variability. The fact that many of these markers are mechano-sensitive offers the opportunity to enhance the diagnostic performance of biomarkers by introducing a stimulus-response paradigm where a mechanical stimulus is used to induce a change in biomarker levels.

Cartilage oligomeric matrix protein (COMP), a marker of cartilage turnover, has been linked to mechanical loading and is well suited to test a stimulus-response paradigm. While COMP levels have been related to OA severity and progression-assessed with either radiographic changes in joint space width or WOMAC scores—a large inter-subject variation precludes the ability to use single measurements of COMP concentration to predict OA progression. However, consistent effects of a mechanical stimulus during a 30-minute walk on serum COMP concentrations represents an opportunity to evaluate the stimulus-response paradigm. Thus, the purpose of this study was to test the hypothesis that changes in COMP levels induced by a mechanical stimulus (30-minute walk) at baseline are correlated with changes in cartilage thickness over a 5-year period.

METHODS:
Patients with medial compartment knee OA (4 male, 6 female; age: 60.1±7.8 yrs; BMI: 29.2±4.3 kg/m²; baseline KL grade: 2.3±1.2; 5 year follow-up KL grade: 3.1±0.9) were tested twice with a mean time between testing of 53 months following written consent in accordance with the Institutional Review Board. MR images of their index knee were acquired at baseline and at 5-year follow-up with a 1.5T scanner (General Electric) using a 3D spoiled gradient-echo sequence in the sagittal plane. Images were manually segmented and 3D cartilage thickness maps were created. For local thickness analysis, the weight-bearing medial femoral cartilage was divided into three sub-regions: external, central, and internal (Figure 1). Similarly, the medial tibia cartilage was divided in five sub-regions: central, anterior, external, posterior, and internal (Figure 1). Cartilage thickness changes were expressed as the difference between the 5-year test and baseline.

At the baseline test, serum COMP concentrations were determined immediately before (resting), immediately after, 3.5, and 5.5 hours after a 30-minute walking exercise using a commercial enzyme-linked immunosorbent assay (COMP ELISA; AnaMar Medical AB, Lund, Sweden). Change in COMP concentration compared to baseline was tested using paired two-tailed Student’s T-tests (P=0.05). Linear regression was used to detect a correlation between changes in cartilage thickness (5-year to baseline) and COMP levels (with post-activity concentrations expressed as a percentage of pre-activity level), and the level of significance was set at P<0.05, with trends defined as P < 0.1.

RESULTS:
Compared to baseline pre-activity levels, serum COMP values increased after the 30-minute walk (+5.3%, P=0.02) and decreased 5.5-hours after activity (-16.7%, P=0.02). No significant differences were seen 3.5 hours after activity (+5.5%, P=0.40). While baseline pre-activity COMP levels did not predict cartilage changes after 5-years, the changes in COMP in response to the mechanical stimulus at baseline predicted the amount of cartilage thinning at the 5-year follow-up. Specifically, changes in COMP levels from resting to immediately after the 30-minute walking activity were negatively associated with changes in cartilage thickness in the internal femoral cartilage (R² = 0.58, P=0.08). In addition, changes in COMP levels between resting and 3.5 hours post-activity were negatively associated with changes in cartilage thickness in the external femoral cartilage (R² = 0.62, P=0.06), central (R² = 0.68, P=0.03), and total (R² = 0.71, P=0.02) femoral cartilage. Similar associations were observed for the anterior (R² = 0.67, P=0.04) and external (R² = 0.69, P=0.03) tibia. Finally, changes in COMP levels between resting and 5.5 hours post-activity were negatively associated with changes in cartilage thickness in the central (R² = 0.66, P=0.04), internal (R² = 0.59, P=0.08) and total (R² = 0.65, P=0.04; Figure 2) medial femoral cartilage and in the anterior (R² = 0.54, P=0.1) and external (R² = 0.59, P=0.08) tibia.

DISCUSSION:
The results of this study support the hypothesis that a change in COMP concentration (ΔCOMP) induced by a mechanical stimulus can predict cartilage thinning (ΔCartilage) in a 5-year follow-up study. A decrease in COMP concentration compared to pre-activity levels may indicate diminished cartilage metabolism hours after the exercise. While only ten patients were included in this initial analysis, the fact that for all time points and all cartilage regions, greater cartilage thinning was associated with less reduction in COMP concentration suggests that the results describe a real phenomenon. Hence, mechanically-induced changes in biomarker concentrations rather than single biomarker concentrations should be further explored in the search for diagnostic tools for OA presence and progression in patients with OA and in people who are at higher risk for OA.

SIGNIFICANCE:
A stimulus-response model may be more sensitive in detecting changes in OA disease progression than single measurements of biomarkers that are sensitive to mechanical stimuli.

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REFERENCES: