Biomarkers

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KNEE OSTEOARTHRITIS PROGRESSION DURING 6 YEARS FOLLOW-UP: THE PROGNOSTIC VALUE OF BONE AND CARTILAGE BIOMARKERS

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Purpose: To investigate the prognostic value of bone-cartilage biomarkers in predicting knee OA progression during 6 years follow-up.
Methods: A population cohort aged 35-55 years (n=141) was investigated at baseline and after 3 and 6 years follow-up. Tibiofemoral (TF) and patellofemoral (PF) radiographs were graded for OA. Progression was documented if presence of osteophytes and/or joint space narrowing (JSN) was described in subjects with no previous radiographic changes or in case of radiographic deterioration during 6 years. At baseline and at 3 years follow-up, biomarkers of bone resorption (CTx-I), - formation (PINP), osteocalcin (OC) were assessed by ECLIA and cartilage oligomeric matrix protein (COMP) - by ELISA. Specific markers of cartilage degradation (U-CTx-II) and synthesis (PIIANP) were assayed by ELISA only at 3-years follow-up. For statistics non-parametric methods were used.
Results: Within 6 years follow-up, progression in TF joint was observed in 38% of cases, mostly from OA grade 0 to 1. At 3 years follow-up we documented radiographic OA progression in 16 men and 38 women out of 141, and at 6 years follow-up in 21 men and 49 women out of 131. In women, the progression in TF osteophytes during 6 year follow-up was related to higher levels of COMP compared to non-progressors (p=0.011). The higher COMP, OC and U-CTx-II levels in case of TF osteophyte progression was found already at 3 years follow-up.
The women who developed TF JSN progression had lower PINP and higher PIIANP levels compared to non-progressors (p levels 0.030 and 0.031, respectively). Progression in PF JSN was related to higher COMP and U-CTx-II values (p levels 0.047 and 0.003, respectively). Increased U-CTx-II levels was found in women who had progression in TFOA and PFOA simultaneously (p=0.030).
Baseline PINP levels were higher in those who developed TFOA and PFOA during 6 years follow-up (p=0.007). Baseline CTx-I levels were higher in case of PF osteophyte progression (p=0.037).
In men, the progression in TF and PF osteophytes was related to higher levels of COMP (p levels 0.003 and 0.025, respectively). The progression in PF osteophytes during 6 years was related to the increase in PIIANP (p=0.019). The progression in JSN was associated with lower OC levels (p=0.045).
Conclusions:

- The 6 years follow-up demonstrated changes in radiographic stage as well as in the levels of the set of biomarkers.
- The pattern of biomarkers differed by gender.
- In both genders, S-COMP levels that reflect the status of several soft joint tissues was associated with the development of TF osteophytes.
- In women, increased degradation of articular cartilage based on U-CTx-II associated with progression in PF JSN. The same process was found in cases when TFOA and PFOA progression was combined.
- Increased synthesis of articular cartilage based on S-PIIANP was related to progression in TF JSN that might refer to enhanced reparative process.
- The activation of bone metabolism was demonstrated in future knee OA progressors already at baseline by the increase in osteoblast-related biomarkers S-OC and S-PINP.

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SERUM CARTILAGE OLIGOMERIC MATRIX PROTEIN (COMP) AND INCIDENT AND PROGRESSIVE RADIOGRAPHIC OSTEOARTHRITIS: THE JOHNSTON COUNTY OSTEOARTHRITIS PROJECT

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Purpose: In our prior cross-sectional analyses, elevated serum cartilage oligomeric matrix protein (COMP) levels were associated with the presence and severity of knee and knee plus hip radiographic osteoarthritis (rOA). This analysis longitudinally examines the usefulness of serum COMP as a predictor of incident and progressive knee and hip rOA in a subsample of a bi-racial county-based population.
Methods: Baseline serum COMP levels were available for 802 participants in the Johnston County Osteoarthritis Project. Serum COMP was measured using an in-house sandwich enzyme linked immunosorbent assay with 5.8-6.6% intra-assay variability and 8.7-9.7% inter-assay variability. Paired baseline and follow-up films for the knee and hip were available for 359 and 338 individuals, respectively. Incident rOA was defined as: 1) development of K-L grade $\geq$2 in a joint with K-L grade $<$2 at baseline, and 2) development of K-L grade $\geq$1 in a joint with K-L grade=0 at baseline. Progression of rOA was defined as: 1) an increase by $\geq$1 K-L grade in a joint that was a K-L grade $\geq$2 at baseline, and 2) an increase by $\geq$1 K-L grade in a joint that was a K-L grade $\geq$1 at baseline. Incident osteophytes (OST) and joint space narrowing (JSN) were identified in a joint with an OST or JSN grade of 0 at baseline and $\geq$1 at follow-up. Progressive OST and JSN was defined as at least 1 grade increase in a joint with an OST or JSN grade $\geq$1 at baseline. The natural logarithm transformation of COMP (lnCOMP) was used to produce a near-normal distribution for analyses. Multivariable Weibull regression models (accounting for varying follow-up times) were used to provide hazard ratios (HR) for each one-unit increase in lnCOMP with rOA outcomes, clustering by individual.
Results: Among participants with paired film and COMP data, mean age was 61.6 ($\pm$ 9.7) years, mean body mass index was 30.3 ($\pm$ 6.8) kg/m^2, 62.7% were female, and 43.5% were African American. Mean serum COMP was 1059.8 ($\pm$600.8) ng/ml (range 170.3-4634.9 ng/ml). Mean time of follow-up was 6.2 ($\pm$1.4) years (range 3-10 years). In unadjusted models, higher lnCOMP was associated with an increased HR of nearly 60% for incidence of knee JSN (HR= 1.59, 95% confidence interval [CI] 0.98-2.58, p=0.06) and approximately 90% for incidence of hip JSN (HR= 1.88, 95% CI 0.99-3.57, p=0.06). Associations were not statistically significant after adjusting for age, body mass index, gender, and race (knee JSN: adjusted HR= 1.31, 95% CI 0.75-2.30; hip JSN: adjusted HR= 2.03, 95% CI 0.90-4.58). No statistically significant associations were noted for other incident or progressive rOA knee and hip outcomes. No interactions of lnCOMP with race or gender were observed in any model (p $>$0.10).
Conclusions: Higher serum COMP may be associated with incident knee and hip rOA, particularly with incident JSN, but the association may be influenced by other risk factors. No association was observed with progression of knee or hip rOA.