

Associations Between Biomarkers of Joint Metabolism, Hand Osteoarthritis, and Hand Pain and Function: The Johnston County Osteoarthritis Project

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ABSTRACT. Objective. To determine the associations between joint metabolism biomarkers and hand radiographic osteoarthritis [rOA), based on Kellgren Lawrence (KL) grade ≥ 2], symptoms, and function.

Methods. Cross-sectional data were available for 663 participants (mean age 63 yrs, 63% white, 49% women). Three definitions of hand rOA were considered: (1) a composite measure involving at least 3 hand joints distributed bilaterally with 2 of 3 in the same joint group, including ≥ 1 distal interphalangeal joint, without metacarpophalangeal (MCP) swelling; (2) rOA in at least 1 joint of a group; and (3) number of joints with KL ≥ 2 . We assessed hand symptoms and the 15-item Australian Canadian Hand Osteoarthritis Index (AUSCAN; Likert format). We measured serum cartilage oligomeric matrix protein (sCOMP), hyaluronic acid (sHA), carboxy-terminal propeptide of type II collagen, type II collagen degradation product, urinary C-terminal crosslinked telopeptide of type II collagen, and urinary N-terminal crosslinked telopeptide. Linear regression models were performed to assess associations between each biomarker with hand rOA, AUSCAN, and symptoms, adjusting for age, sex, race, current smoking/drinking status, body mass index, and hip and knee rOA.

Results. In adjusted analyses, MCP ($p < 0.0001$) and carpometacarpal rOA ($p = 0.003$), and a higher number of hand joints with rOA ($p = 0.009$), were associated with higher levels of sHA. Positive associations were seen between AUSCAN and hand symptoms and levels of sCOMP ($p \leq 0.003$) and sHA ($p \leq 0.048$).

Conclusion. Hand symptoms and higher AUSCAN scores were independently associated with higher levels of both sCOMP and sHA; hand rOA was associated only with sHA levels. (First Release March 1 2014; J Rheumatol 2014;41:938–44; doi:10.3899/jrheum.130904)

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RADIOGRAPHY

Radiographic osteoarthritis (rOA) of the hand is extremely common, occurring in about half of adults over age 55^{1,2}. Symptomatic hand OA is less frequently seen, with estimates in the range of 3–8% of older adults^{2,3}. Functional limitations and disability related to hand OA can be

substantial^{4,5,6,7}, even for “asymptomatic” rOA⁸. The multiple possible joints involved and varying patterns of joint involvement lead to various definitions of what constitutes hand OA, making it difficult to compare studies and outcomes. Alternate methods of assessing hand OA, such as

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the use of biomarkers, could provide a quantitative measure of OA and assist in characterizing clinically relevant aspects of the hand OA pathophysiologic process.

Biomarkers are a promising alternative means of diagnosing and monitoring OA early in the disease process and may have the potential to predict the development and progression of OA⁹. Several biomarkers have been identified as indicators of OA involvement at commonly affected large joint sites such as the knee and hip^{9,10,11,12}. Regarding hand OA, Kraus, *et al* examined systemic biomarker levels with total body burden of OA in women and found that some hand joint groups, particularly carpometacarpal (CMC), contributed disproportionately to specific biomarker measurements¹³. Hyaluronic acid, found in cartilage and connective tissue throughout the body, was elevated in women with erosive hand rOA in comparison to those with nonerosive forms^{14,15}. A marker of cartilage catabolism was elevated in erosive and nodal OA compared with controls, although no markers were different between patients with erosive and patients with nodal OA¹⁶. Several inflammatory factors [C-reactive protein, tumor necrosis factor- α , interleukins, and metacarpophalangeal (MCP)-1, among others] have also been linked to hand rOA^{17,18,19}, although these findings have not been consistent^{15,20}. Using principal components analysis, the Genetics of Osteoarthritis and Progression (GARP) study has identified associations between hand OA and several biomarkers including urinary C-terminal crosslinked telopeptide of type II collagen (uCTX-II) and serum cartilage oligomeric matrix protein (COMP)²¹. CTX-II may also be useful in monitoring treatment response in hand OA²². Many of these studies were small and/or had limited data on OA at other joint sites, which is highly relevant because OA at other joint sites may contribute to systemically measured biomarkers in serum and urine.

The aim of our study was to improve understanding of associations between biomarkers and hand OA, to inform future work on specific aspects of biomarkers in hand OA, such as diagnostic and prognostic performance characteristics. Our present study was designed to explore associations between 6 systemic biomarkers of joint metabolism reflecting bone, cartilage, and synovial involvement and several radiographic and clinical manifestations of hand OA in a relatively large sample of white and African American men and women from the Johnston County Osteoarthritis Project (JoCo OA).

MATERIALS AND METHODS

Participants in our study were from the JoCo OA, an ongoing community-based study of OA and its risk factors. As reported, this well-characterized cohort includes noninstitutionalized individuals, aged 45 years and older, from 6 selected townships in Johnston County, North Carolina, USA²³. The biomarkers substudy was performed from 2003–2008 on a subset of participants ($n = 671$) selected to represent a balance by sex (50% female) and to include a large proportion of African Americans (37%)²⁴. Participants with radiographic evidence of rheumatoid

arthritis were excluded. This analysis includes those participants in the substudy who had data for at least 1 biomarker ($n = 661$), body mass index (BMI; $n = 662$), the AUSCAN index ($n = 658$), and hand rOA ($n = 638$). The JoCo OA has been continuously approved by the institutional review boards of the US Centers for Disease Control and Prevention and the University of North Carolina at Chapel Hill.

Demographic and clinical characteristics. Self-reported sex, race (white or African American), age, current smoking (yes/no), and current drinking status (yes/no) were collected during home interviews. Height without shoes was measured in centimeters, and weight was measured in kilograms with a balance beam scale during the clinic assessment. BMI was calculated as weight in kg/height in meters squared. Hand symptoms were assessed by the US National Health and Nutrition Examination Survey (NHANES) I question²⁵ “On MOST days, do you have pain, aching, or stiffness in your hands?”

Australian Canadian Hand Osteoarthritis Index (AUSCAN). AUSCAN is a valid and reliable self-report 15-item questionnaire that assesses hand symptoms in those with and without hand rOA^{26,27}. AUSCAN was administered using the Likert format by trained interviewers in the JoCo OA to evaluate hand pain, stiffness, and function experienced in the 2 days before. There are 5 items for pain, 1 for stiffness, and 9 for function, addressing symptoms experienced during various activities such as gripping, lifting, or turning objects, and about difficulties with activities such as opening new jars or fastening clothes or jewelry. Each item is scored from 0 (none) to 4 (extreme), yielding a total possible score of 60, with higher scores indicating worse pain and function.

Bone and joint tissue biomarker assays. Blood for serum and second morning void urine samples were obtained and then stored at -86°C , as reported²⁴.

Osteomark NTX Urine kit was used to measure levels of urine NTX-I (cross-linked N telopeptide of type I collagen). A competitive-inhibition ELISA was used with reported precision of 7.6% intraassay and 4.0% interassay variability (Osteomark Performance data online at www.osteomark.com). Final results were corrected for urine creatinine concentration.

The biomarker CTX-II (urinary C-telopeptide fragments of type II collagen) was measured with the Urine Cartilaps competitive ELISA. The reported precision was between 4.6–7.8% intraassay and 6.9–12.2% interassay variability. Final results were corrected for urine creatinine concentration.

For serum COMP, a sandwich ELISA was used with precision between 5.8–6.6% intraassay and 8.7–9.7% interassay variability²⁸.

Collagen type II cleavage ELISA (Ibex Pharmaceuticals) was used to measure serum C2C (collagenase-generated cleavage neoepitope of type II collagen). This ELISA has a precision of 9.7% intraassay²⁹ and < 20% interassay variability (Ibex data sheet).

To measure levels of serum CPII (type II collagen c-propeptide), the Procollagen II C-Propeptide ELISA (Ibex) was used. The precision was 6.4% intraassay²⁹ and < 25% interassay variability (Ibex).

The Hyaluronic Acid Test kit (Corgenix), an enzyme-linked binding protein assay, was used to measure serum HA (SHA, hyaluronan) levels. The precision was < 5% intraassay and < 7.0% interassay variability.

Radiographic assessment. Bilateral posteroanterior radiography of the hands and of the knees in fixed flexion ($\sim 20^{\circ}$) and weight-bearing was conducted for all participants. All men and women over 50 years had a supine anteroposterior pelvic radiograph. A single musculoskeletal radiologist (JBR) read all radiographs with high intrarater reliability (weighted κ 0.9)²³. Radiographs were assessed using the Kellgren-Lawrence (KL) radiographic atlas for knee, hip, and hand, with a KL score of 2 or more used to define rOA³⁰.

Hand rOA was defined primarily using the Genetics of Generalized Osteoarthritis (GOGO) definition³¹, as a KL grade ≥ 2 involving at least 3 hand joints [distal and proximal interphalangeal (DIP and PIP), or CMC] distributed bilaterally with 2 of 3 in the same joint group, including at least

1 DIP, and without MCP swelling on physical examination. We also explored alternative definitions including joint group, where hand rOA was present in at least 1 joint (DIP, PIP, MCP, or CMC) of a joint group (e.g., if at least 1 DIP had a KL ≥ 2 , the criteria for DIP rOA were met); and the total number of hand joints affected by hand rOA across both hands (range 0–30).

Statistical analysis. Descriptive statistics were calculated for the whole sample and also for subgroups of interest (e.g., GOGO hand rOA). Frequencies and percentages were computed for categorical variables (sex, race, smoking, drinking, knee rOA, hip rOA, and hand rOA variables) and the median and total range for continuous variables [age, BMI, AUSCAN, and each biomarker: uNTX-I, uCTX-II, sCOMP, sC2C, sCPII (C2C:CPII), and sHA]. For AUSCAN, we focused on the total score, because the results were similar for the total score and the individual pain and function subscales, although those values are also mentioned in the text. Chi-square statistics for categorical variables and 1-way ANOVA testing of linear trend for continuous variables were used to compare hand OA and non-hand OA groups. Spearman partial correlation coefficients were examined between the AUSCAN total score and each biomarker and between the individual biomarkers.

Separate multiple linear regression models were used to examine the associations between each of the natural logarithm–(ln)–transformed biomarkers and each of the main hand OA variables of interest (GOGO hand rOA, DIP rOA, PIP rOA, MCP rOA, CMC rOA, number of joints with hand rOA, AUSCAN total score, and hand symptoms). Ln-transformation allowed the distribution of each biomarker to approximate a normal distribution; these transformed values were used in the models. Based on *a priori* hypotheses regarding potentially important confounders, regression

models were adjusted for age and BMI as continuous variables, and categorical race, sex, smoking, drinking, and rOA status in the knee and hip. We also explored stratification by race for GOGO hand rOA and hand symptoms. Those models evaluating associations between biomarkers and the AUSCAN were additionally adjusted for GOGO hand rOA. A Bonferroni correction was applied to the p values from the final model, adjusting for 8 models (8 different main hand variables) per biomarker outcome.

Each of the adjusted regression models started with a full model including all 2-way interactions between the main hand OA variable and the adjusting covariates, as well as the polynomials of the continuous main hand OA variables (number of hand joints and AUSCAN total score) up to the third power. At that point, backward selection was conducted to remove 1 interaction, or the highest order polynomial term, at a time, until all $p < 0.1$. A p value < 0.1 for an interaction term was considered noteworthy for potential effect modification; based on this criterion, no interactions were identified. Owing to a large number of individuals with a “0” value for AUSCAN, we explored categorizing AUSCAN total into tertiles, quartiles, and quintiles with similar results; we report the results using tertiles (tertile 1 = 0, tertile 2 range 1–10, and tertile 3 range 11–53), which divided the sample most evenly.

RESULTS

Demographic and clinical characteristics, overall and by GOGO hand rOA status, are shown in Table 1. Participants had a median age of 63 years and BMI of 29 kg/m². About

Table 1. Characteristics of the study population overall and by GOGO Hand rOA* status (n = 638). P value for comparison between groups with and without GOGO Hand rOA; values in boldface are statistically significant.

Characteristic	Overall, n = 638		With GOGO Hand rOA, n = 163		Without GOGO Hand rOA, n = 475		p
	n or median	% or (range)	n or median	% or (range)	n or median	% or (range)	
Women	325	50.94	86	52.76	239	50.32	0.590
White	401	62.85	138	84.66	263	55.37	< 0.0001
Current smoker	129	20.22	19	11.66	110	23.16	0.002
Alcohol drinker	180	28.21	35	21.47	145	30.53	0.027
Knee rOA	225	35.32	102	62.96	123	25.89	< 0.0001
Hip rOA	165	26.15	67	41.88	98	20.81	< 0.0001
Hand symptoms (yes/no)	281	44.19	84	51.53	197	41.65	0.028
GOGO Hand rOA*	163	25.55	—	—	—	—	—
DIP rOA	255	39.97	163	100	92	19.37	< 0.0001
PIP rOA	204	31.97	131	80.37	73	15.37	< 0.0001
MCP rOA	65	10.85	44	29.73	21	4.66	< 0.0001
CMC rOA	140	21.94	89	54.60	51	10.74	< 0.0001
No. hand joints w/rOA	1	(0, 20)	7	(3, 20)	0	(0, 5)	< 0.0001
Age, yrs	62.08	(45.00, 91.83)	71.92	(52.50, 91.83)	59.50	(45, 87)	< 0.0001
BMI, kg/m ²	29.56	(15.06, 54.39)	28.89	(18.36, 51.03)	29.76	(15.06, 54.39)	0.958
AUSCAN Total†	3	(0, 53)	5	(0, 53)	3	(0, 51)	0.059
uNTX-I, nmol BCE/mmol Cr	56.33	(5.92, 4214.72)	59.50	(10.17, 362.60)	55.91	(5.92, 4214.72)	0.599
uCTX-II, ng/mmol Cr	214.43	(8.09, 2705.01)	245.13	(10.84, 1310.90)	203.42	(8.09, 2705.01)	0.025
sCOMP, ng/ml	1448.81	(339.32, 7279.05)	1435.60	(439.94, 5668.76)	1448.85	(339.32, 7279.05)	0.433
sC2C, ng/ml	172.65	(54.00, 1060.20)	172.80	(54.00, 317.80)	172.39	(65.00, 1060.20)	0.934
sCPII, ng/ml	914.44	(227.96, 2991.30)	937.47	(277.26, 2991.30)	895.85	(227.96, 2352.10)	0.766
Ratio sC2C/CPII	0.19	(0.04, 0.76)	0.19	(0.04, 0.55)	0.19	(0.06, 0.76)	0.820
sHA, ng/ml	24.29	(0.11, 707.81)	33.85	(0.64, 391.26)	21.92	(0.11, 707.81)	< 0.0001

*GOGO Hand rOA: KL grade ≥ 2 involving at least 3 hand joints [distal and proximal interphalangeal (DIP and PIP), carpometacarpal (CMC)] distributed bilaterally with two-thirds in the same group, including at least 1 DIP, and without metacarpophalangeal (MCP) swelling on physical examination¹.

†AUSCAN total score: sum of 15 items with range 0–4, maximum possible score of 60. GOGO: Genetics of Generalized Osteoarthritis study; rOA: radiographic osteoarthritis; BMI: body mass index; AUSCAN: Australian Canadian Hand Osteoarthritis Index; uNTX-I: urine cross linked N telopeptide of type I collagen; BCE: bone collagen equivalent; uCTX-II: urine C-terminal crosslinked telopeptide of type II collagen; sCOMP: serum cartilage oligomeric matrix protein; sC2C: serum type II collagen degradation product; sCPII: serum carboxy-terminal propeptide of type II collagen; sHA: serum hyaluronic acid.

two-thirds of all participants were white and half were women. There were 20% current smokers and 28% current alcohol drinkers. Knee rOA was present in about one-third of the sample, while hip rOA and GOGO hand rOA were present in about one-quarter. DIP and PIP rOA were identified in 40% and 32%, respectively, while 11% had MCP rOA and 22% had CMC rOA; the median number of hand joints affected was 1 (range 0–20). The median total AUSCAN score was 3, with a range from 0 to 53. Hand symptoms were present in 44% of the sample. Those participants with hand rOA by the composite GOGO definition were older, more often white, less likely to be current smokers or alcohol drinkers, more likely to have concomitant knee or hip rOA, more likely to report hand symptoms, and had a slightly higher AUSCAN score (Table 1).

The levels of each biomarker overall and by GOGO hand rOA are also shown in Table 1. Urinary CTX-II and sHA levels were higher in those with hand rOA compared to those without; levels of the other biomarkers were not statistically significantly different. AUSCAN total score was positively associated with levels of sCOMP ($p = 0.006$), and there was a borderline association with sHA ($p = 0.057$, Table 2). Statistically significant crude associations were also seen between hand symptoms and uNTX-1 and sCOMP, and between AUSCAN and uNTX-1 and sCOMP (data not shown).

sCOMP. In models adjusted for rOA in the hands, knees, or hips and demographics (Table 3), ln sCOMP was significantly higher in those participants in the highest tertile of AUSCAN score (> 11) compared to those with an AUSCAN total score of 0 (the lowest tertile), such that the ln sCOMP level would be 0.13 units higher in an individual with a highest tertile AUSCAN score compared with an individual in the lowest AUSCAN tertile. Similar results were

observed for AUSCAN pain (β 0.14, $p = 0.003$) and function (β 0.10, $p = 0.025$) subscales, and hand symptoms (β 0.11, $p = 0.001$). The association between ln sCOMP and hand symptoms was similar among African American and white participants in stratified analyses. After adjustment for rOA in the knees and hips, there were no significant associations of ln sCOMP and any of the hand rOA variables.

sHA. In models adjusted for rOA in the hands, knees or hips, and demographics (Table 3), ln sHA was also significantly higher (by 0.18 units) in those participants in the highest tertile of AUSCAN score compared to those in the lowest tertile. Similar results were observed for the AUSCAN pain (β 0.16, $p = 0.056$) and function (β 0.10, $p = 0.076$) subscales, and hand symptoms (β 0.16, $p = 0.034$). Ln sHA was positively associated with presence of MCP or CMC rOA, such that ln sHA was 0.55 units higher in those with MCP rOA than in those without, and 0.30 units higher in those with CMC rOA versus those without. Also, for each additional hand joint with rOA (0–30), there was a small but statistically significant increase in ln sHA (β 0.03, 95% CI 0.01–0.05, $p = 0.009$). There was no association between sHA and presence of DIP or PIP rOA, or GOGO hand rOA, and results were similar in analyses stratified by race.

Associations between ln sCOMP and AUSCAN and hand symptoms, and ln sHA and MCP rOA and CMC rOA remained significant after Bonferroni adjustment (Table 3). There were no other statistically significant associations between hand variables and biomarkers; specifically, the association between uNTX-I and AUSCAN was no longer statistically significant in adjusted models. Additional analyses restricted to a smaller age range (because of observed age differences in those with and without GOGO rOA) were similar to those of the full sample (data not shown). Stratification by race, although limited by smaller sample size, revealed a borderline association between GOGO rOA and uNTX-I ($p = 0.08$) among African Americans and between GOGO rOA and uCTX-II among whites ($p = 0.07$).

DISCUSSION

In this analysis of biomarker and hand OA data from a community-based cohort, we found higher levels of sCOMP and sHA to be associated with higher total AUSCAN scores and hand symptoms, independent of rOA in the knees and hips. Also independent of other covariates including age and knee and hip rOA, sHA levels were higher in participants with MCP or CMC rOA, and for greater numbers of hand joints affected by rOA. Knee rOA demonstrated statistically significant associations with sHA (as previously shown in this cohort¹⁰) and with uCTX-II, but not with other biomarkers, and no associations were seen between biomarkers and hip rOA in models including hand variables. Overall, sCOMP levels primarily reflected hand pain and function rather than structural alterations of OA, while sHA

Table 2. Spearman partial correlation coefficients (adjusted*) between individual biomarkers and AUSCAN total score ($n = 663$).

Biomarker*	Spearman Partial CC	p
uNTX-I	0.01	0.760
uCTX-II	0.02	0.660
sCOMP	0.11	0.006
sC2C	0.05	0.221
sCPII	0.04	0.284
Ratio	−0.03	0.409
sHA	−0.08	0.057

* Adjusted for age, sex, smoking, drinking, knee and hip rOA, and GOGO hand rOA. AUSCAN: Australian Canadian Hand Osteoarthritis Index; rOA: radiographic osteoarthritis; GOGO: Genetics of Generalized Osteoarthritis study; CC: correlation coefficient; uNTX-I: urine crosslinked N telopeptide of type I collagen; uCTX-II: urine C-terminal crosslinked telopeptide of type II collagen; sCOMP: serum cartilage oligomeric matrix protein; sC2C: serum type II collagen degradation product; sCPII: serum carboxy-terminal propeptide of type II collagen; ratio: C2C/CPII; sHA: serum hyaluronic acid.

Table 3. Summary of adjusted associations between biomarkers, 3 definitions of hand rOA, AUSCAN scores, and hand symptoms*. Data are β (95% CI). Numbers in boldface are statistically significant.

	1. GOGO [†] GOGO rOA	DIP rOA	2. Joint Group [†] PIP rOA	MCP rOA	CMC rOA [†]	3. No. Joints [†]	4. AUSCAN [‡]	5. Symptoms Hand pain, aching, stiffness
uNTX-I	-0.07 (-0.21, 0.08)	-0.002 (-0.13, 0.12)	-0.09 (-0.22, 0.04)	-0.02 (-0.21, 0.18)	-0.04 (-0.18, 0.10)	-0.01 (-0.03, 0.003)	0.06 (-0.07, 0.20)	-0.13 (-0.11, 0.09)
p	0.381	0.974	0.154	0.875	0.568	0.121	0.350	0.805
uCTX-II	0.12 (-0.03, 0.28)	0.11 (-0.02, 0.24)	0.12 (-0.01, 0.26)	0.07 (-0.13, 0.27)	0.05 (-0.09, 0.19)	0.001 (-0.01, 0.02)	-0.01 (-0.15, 0.13)	0.03 (-0.08, 0.14)
p	0.111	0.108	0.077	0.498	0.499	0.738	0.850	0.614
sCOMP	0.02 (-0.07, 0.12)	-0.02 (-0.11, 0.06)	-0.01 (-0.10, 0.08)	0.03 (-0.15, 0.09)	0.06 (-0.03, 0.15)	-0.002 (-0.01, 0.01)	0.13 (0.05, 0.22)	0.11 (0.05, 0.19)
p	0.623	0.563	0.821	0.678	0.192	0.719	0.003[§]	0.001[§]
sC2C	-0.01 (-0.07, 0.05)	-0.03 (-0.08, 0.02)	-0.01 (-0.07, 0.05)	0.05 (-0.03, 0.13)	0.02 (-0.04, 0.07)	-0.001 (-0.01, 0.01)	-0.01 (-0.06, 0.05)	-0.01 (-0.04, 0.04)
p	0.762	0.216	0.762	0.185	0.606	0.925	0.864	0.983
sCPII	-0.01 (-0.09, 0.07)	0.01 (-0.06, 0.08)	-0.01 (-0.09, 0.06)	0.05 (-0.06, 0.16)	0.02 (-0.06, 0.10)	-0.002 (-0.01, 0.01)	0.06 (-0.02, 0.13)	-0.01 (-0.08, 0.05)
p	0.799	0.777	0.736	0.407	0.578	0.680	0.164	0.682
C2C:CPII	0.002 (-0.09, 0.09)	-0.04 (-0.12, 0.03)	-0.01 (-0.09, 0.07)	0.01 (-0.11, 0.13)	-0.01 (-0.09, 0.08)	0.002 (-0.01, 0.01)	-0.06 (-0.14, 0.02)	0.013 (-0.05, 0.08)
p	0.969	0.273	0.826	0.913	0.861	0.741	0.151	0.708
sHA	0.06 (-0.15, 0.26)	-0.004 (-0.18, 0.17)	0.16 (-0.03, 0.34)	0.55 (0.28, 0.82)	0.30 (0.10, 0.49)	0.03 (0.01, 0.05)	0.18 (0.01, 0.38)	0.16 (0.01, 0.31)
p	0.602	0.963	0.096	<0.0001[§]	0.003[§]	0.009	0.048	0.034

* Each model included 1 biomarker as the outcome and 1 hand variable with the exception of AUSCAN models, which were additionally adjusted for GOGO rOA. [†]Hand OA models include adjustment for continuous age and BMI, categorical race and sex, smoking/drinking status, knee and hip rOA. [‡]AUSCAN total cutoffs: tertile 1 (0–0); tertile 2 (1–10); tertile 3 (11–53); given are values for Q3 versus Q1. Models include adjustment for continuous age and BMI, categorical race and sex, smoking/drinking status, knee and hip rOA, and GOGO hand rOA. [§]Statistically significant after Bonferroni adjustment for 8 models per biomarker ($p \leq 0.006$). GOGO: Genetics of Generalized Osteoarthritis study; rOA: radiographic osteoarthritis; AUSCAN: Australian Canadian Hand Osteoarthritis Index; uNTX-I: urine cross linked N telopeptide of type I collagen; DIP: distal interphalangeal; PIP: proximal interphalangeal; MCP: metacarpophalangeal; CMC: carpometacarpal; uCTX-II: urine C-terminal crosslinked telopeptide of type II collagen; sCOMP: serum cartilage oligomeric matrix protein; sC2C: serum type II collagen degradation product; sCPII: serum carboxy-terminal propeptide of type II collagen; sHA: serum hyaluronic acid.

levels reflected both symptomatic and structural change in hand OA. Our present study, focused on hand OA, supports evidence identifying both HA and COMP as a burden of disease biomarkers by the Burden of Disease, Investigative, Prognostic, Efficacy of Intervention, and Diagnostic (BIPED) criteria³².

The strongest association in our analysis was between MCP rOA and sHA. Several studies have shown that the MCP joints are commonly affected by rOA^{1,2,31}. More than 36% of the participants in the GOGO study had radiographic MCP involvement³¹, similar to a study of participants from Framingham in which 29–33% had MCP rOA². Although only 8% of Rotterdam Study participants had MCP rOA, it was commonly seen in conjunction with other hand joint involvement (86% of those with MCP rOA had other hand joint rOA)¹. This high prevalence of OA at MCP joints is likely underappreciated because the changes on radiographs are not readily apparent on clinical examination. Associations between joint space narrowing at the MCP and both sHA and sCOMP have been reported; sCOMP was also associated with osteophytes at this joint

site¹³. The MCP joints may be an early site of hand OA, occurring prior to changes in other joints as suggested by Kalichman, *et al*³³, potentially making this site more prone to inflammation and damage associated with HA release.

COMP is found predominately in articular cartilage and is released into the serum as a result of cartilage turnover (damage and repair)³⁴. The literature contains many studies that examine the relationship between sCOMP and knee or hip OA^{9,28,34}; however, there are few studies that explore this relationship in hand OA. Higher sCOMP levels correlate with radiographic knee OA progression²⁸. The levels are higher in those with knee OA compared to those without, and correlate with severity of rOA as well as the number of affected knee and hip joints³⁴. Levels of sCOMP are also associated with the presence of hip rOA and progression of joint space narrowing at the hip³⁵. Chen, *et al* reported sCOMP levels to be significantly higher in subjects with clinically defined hand OA than in subjects without hand OA, although this finding was not independent of age³⁶. Associations have been found between sCOMP and joint space narrowing at the IP and MCP joints (inversely

associated) and MCP osteophytes¹³. Serum COMP, as part of a principal component, was associated with hand rOA score in the GARP cohort²¹. We report an association between sCOMP and clinical hand symptoms based on the AUSCAN total score and the NHANES-based interviewer-administered question, but not hand rOA alone. This may be due to our use of composite KL grades rather than individual radiographic features, or may suggest a “pre-radiographic” stage of OA characterized by elevations in AUSCAN score and hand symptoms. The small joints of the hands have been shown to contribute to systemic biomarker levels, so the lack of apparent association is not likely due to the size of the joints alone¹³.

HA is a glycosaminoglycan found in many joint tissues, and is an important component of articular cartilage and synovium¹⁴. It is a marker for synovitis and joint inflammation and is influenced by a variety of factors such as food intake³⁷, activity levels, and disease³⁸. HA has been considered a promising biomarker for OA diagnosis and disease burden^{13,32,39}. Higher serum levels of HA have been associated with knee KL grades⁴⁰, knee and hip rOA^{10,41,42}, an increased number of affected joints¹⁰, higher total burden of osteophytes¹³, and greater number of joint space narrowing faces in the MCP and CMC joints¹³. In the extended CARRIAGE family study, although not statistically significant, HA was higher among participants with clinically defined hand OA compared to those without³⁶. Individuals with erosive hand OA were reported to have higher systemic levels of HA when compared to those with nonerosive OA; those with radiographic progression of disease had comparatively higher sHA levels¹⁴. In agreement with these studies, we found associations between sHA and rOA at the MCP and CMC, independent of OA at other sites. These data suggest that OA in these joints may involve more synovial inflammation than rOA at other hand joints and/or greater disease severity than other hand joints, confirming that even small joints contribute to systemic biomarker levels. In addition, we found an independent association between sHA and AUSCAN scores, reflecting hand pain and function. Synovitis by magnetic resonance imaging has been associated with hand joint tenderness and functional indices (although not with AUSCAN)⁴³ and is accepted to be a source of pain in knee OA^{44,45}. Therefore, elevated sHA in hand OA may be reflective of early disease with associated hand symptoms.

The many strengths of our analysis include the use of data from a large, well-characterized cohort comprised of African American and white men and women; the availability of radiographs for multiple joint sites; the use of multiple biomarkers; and a relatively large sample size. Limitations include the cross-sectional nature of the analysis (although future longitudinal studies are possible in this cohort), and the lack of hand joint-specific symptoms data at this timepoint. Some of the biomarker assays (for C2C and CPII in

particular) had high variability. We did not have radiographs of additional joint sites that can be affected by OA such as the shoulders or feet, and our radiographic assessments were limited to KL grades and did not include individual features of OA such as osteophytes or joint space narrowing.

This cross-sectional analysis supports the role of sHA and to a lesser extent sCOMP as burdens of disease biomarkers for hand OA. Independent of rOA at the knee or hip, higher levels of both markers were associated with hand symptoms and higher total AUSCAN scores indicating more pain and poorer function, and sHA was also associated with hand rOA. Longitudinal studies are needed to determine the potential diagnostic or prognostic potential and performance of these biomarkers in hand OA.

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