

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

Imran Aslam, Irina Perjar, Xiaoyan A. Shi, Jordan B. Renner, Virginia B. Kraus, Yvonne M. Golightly, Joanne M. Jordan, and Amanda E. Nelson

**ABSTRACT. Objective.** To determine the associations between joint metabolism biomarkers and hand radiographic osteoarthritis [rOA), based on Kellgren Lawrence (KL) grade  $\geq 2$ ], 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  $\geq 1$  distal interphalangeal joint, without metacarpophalangeal (MCP) swelling; (2) rOA in at least 1 joint of a group; and (3) number of joints with KL  $\geq 2$ . 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)

## Key Indexing Terms:

HAND JOINTS

BIOMARKERS

OSTEOARTHRITIS

RADIOGRAPHY

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

substantial<sup>4,5,6,7</sup>, even for “asymptomatic” rOA<sup>8</sup>. 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

From the Northeast Ohio Medical School, Rootstown, Ohio; the School of Medicine, the Thurston Arthritis Research Center, the Department of Radiology, the Department of Epidemiology, and the Department of Orthopedics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill; SAS Institute, Cary; Duke University School of Medicine, Durham, NC, USA.

Funded in part by: Aslam/Perjar: American Geriatrics Society Medical Student Training in Aging Research (MSTAR) program; Perjar: American College of Rheumatology/Rheumatology Research Foundation Medical Student Research Preceptorship; Kraus: US National Institutes of Health (NIH)/National Institute on Aging Claude D. Pepper Older American Independence Centers P60 AG11268 and P30 AG028716, NIH/US National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) U01 AR050898; Jordan/Renner: US Centers for Disease Control and Prevention/Association of Schools of Public Health S043 and S3486, NIH/NIAMS Multidisciplinary Clinical Research Centers P60 AR49465; Golightly: Arthritis Foundation Postdoctoral Fellowship Award; Nelson: NIH/NIAMS K23 AR061406.

I. Aslam, BS, medical student, Northeast Ohio Medical School; I. Perjar, BA, medical student, University of North Carolina at Chapel Hill School

of Medicine; X.A. Shi, PhD, staff statistician, Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, and SAS Institute; J.B. Renner, MD, Professor, Department of Radiology, Thurston Arthritis Research Center and Department of Radiology, University of North Carolina at Chapel Hill; V.B. Kraus, MD, PhD, Professor of Medicine and Pathology, Associate Professor in Surgery, Duke University School of Medicine; Y.M. Golightly, PT, PhD, Assistant Professor of Epidemiology, Thurston Arthritis Research Center, and Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill; J.M. Jordan, MD, MPH, Professor of Medicine and Orthopedics, Adjunct Professor of Epidemiology, School of Medicine, Thurston Arthritis Research Center, Department of Epidemiology, Gillings School of Global Public Health, Department of Orthopedics, University of North Carolina at Chapel Hill; A.E. Nelson, MD, MSCR, Assistant Professor of Medicine, School of Medicine, and Thurston Arthritis Research Center, University of North Carolina at Chapel Hill.

Address correspondence to Dr. A.E. Nelson, University of North Carolina at Chapel Hill, 3300 Doc J. Thurston Building, CB #7280, Chapel Hill, North Carolina 27599-7280, USA. E-mail: aenelson@med.unc.edu

Accepted for publication November 19, 2013.

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 OA<sup>9</sup>. Several biomarkers have been identified as indicators of OA involvement at commonly affected large joint sites such as the knee and hip<sup>9,10,11,12</sup>. 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 measurements<sup>13</sup>. 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<sup>14,15</sup>. 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 OA<sup>16</sup>. Several inflammatory factors [C-reactive protein, tumor necrosis factor- $\alpha$ , interleukins, and metacarpophalangeal (MCP)-1, among others] have also been linked to hand rOA<sup>17,18,19</sup>, although these findings have not been consistent<sup>15,20</sup>. 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)<sup>21</sup>. CTX-II may also be useful in monitoring treatment response in hand OA<sup>22</sup>. 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, USA<sup>23</sup>. 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%)<sup>24</sup>. 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 question<sup>25</sup> “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<sup>26,27</sup>. 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  $-86^{\circ}\text{C}$ , as reported<sup>24</sup>.

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](http://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 variability<sup>28</sup>.

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% intraassay<sup>29</sup> 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% intraassay<sup>29</sup> 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  $\kappa$  0.9)<sup>23</sup>. 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 rOA<sup>30</sup>.

Hand rOA was defined primarily using the Genetics of Generalized Osteoarthritis (GOGO) definition<sup>31</sup>, as a KL grade  $\geq 2$  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  $\geq 2$ , 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/m<sup>2</sup>. 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	<b>&lt; 0.0001</b>
Current smoker	129	20.22	19	11.66	110	23.16	<b>0.002</b>
Alcohol drinker	180	28.21	35	21.47	145	30.53	<b>0.027</b>
Knee rOA	225	35.32	102	62.96	123	25.89	<b>&lt; 0.0001</b>
Hip rOA	165	26.15	67	41.88	98	20.81	<b>&lt; 0.0001</b>
Hand symptoms (yes/no)	281	44.19	84	51.53	197	41.65	<b>0.028</b>
GOGO Hand rOA*	163	25.55	—	—	—	—	—
DIP rOA	255	39.97	163	100	92	19.37	<b>&lt; 0.0001</b>
PIP rOA	204	31.97	131	80.37	73	15.37	<b>&lt; 0.0001</b>
MCP rOA	65	10.85	44	29.73	21	4.66	<b>&lt; 0.0001</b>
CMC rOA	140	21.94	89	54.60	51	10.74	<b>&lt; 0.0001</b>
No. hand joints w/rOA	1	(0, 20)	7	(3, 20)	0	(0, 5)	<b>&lt; 0.0001</b>
Age, yrs	62.08	(45.00, 91.83)	71.92	(52.50, 91.83)	59.50	(45, 87)	<b>&lt; 0.0001</b>
BMI, kg/m <sup>2</sup>	29.56	(15.06, 54.39)	28.89	(18.36, 51.03)	29.76	(15.06, 54.39)	0.958
AUSCAN Total <sup>†</sup>	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)	<b>0.025</b>
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)	<b>&lt; 0.0001</b>

\*GOGO Hand rOA: KL grade  $\geq 2$  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 examination<sup>1</sup>.

<sup>†</sup>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 ( $\beta 0.14$ ,  $p = 0.003$ ) and function ( $\beta 0.10$ ,  $p = 0.025$ ) subscales, and hand symptoms ( $\beta 0.11$ ,  $p = 0.001$ ). 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 ( $\beta 0.16$ ,  $p = 0.056$ ) and function ( $\beta 0.10$ ,  $p = 0.076$ ) subscales, and hand symptoms ( $\beta 0.16$ ,  $p = 0.034$ ). 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 ( $\beta 0.03$ , 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 ( $p = 0.07$ ).

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.

## 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 cohort<sup>10</sup>) 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 3. Summary of adjusted associations between biomarkers, 3 definitions of hand rOA, AUSCAN scores, and hand symptoms\*. Data are  $\beta$  (95% CI). Numbers in boldface are statistically significant.

	1. GOGO <sup>†</sup>		2. Joint Group <sup>†</sup>		3. No. Joints <sup>†</sup>	4. AUSCAN <sup>‡</sup>	5. Symptoms	
	GOGO rOA	DIP rOA	PIP rOA	MCP rOA				CMC rOA <sup>†</sup>
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)	<b>0.13</b> <b>(0.05, 0.22)</b>	<b>0.11</b> <b>(0.05, 0.19)</b>
p	0.623	0.563	0.821	0.678	0.192	0.719	<b>0.003<sup>§</sup></b>	<b>0.001<sup>§</sup></b>
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)	<b>0.55</b> <b>(0.28, 0.82)</b>	<b>0.30</b> <b>(0.10, 0.49)</b>	<b>0.03</b> <b>(0.01, 0.05)</b>	<b>0.18</b> <b>(0.01, 0.38)</b>	<b>0.16</b> <b>(0.01, 0.31)</b>
p	0.602	0.963	0.096	<b>&lt;0.0001<sup>§</sup></b>	<b>0.003<sup>§</sup></b>	<b>0.009</b>	<b>0.048</b>	<b>0.034</b>

\* 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. <sup>†</sup>Hand OA models include adjustment for continuous age and BMI, categorical race and sex, smoking/drinking status, knee and hip rOA. <sup>‡</sup>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. <sup>§</sup>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) criteria<sup>32</sup>.

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<sup>1,2,31</sup>. More than 36% of the participants in the GOGO study had radiographic MCP involvement<sup>31</sup>, similar to a study of participants from Framingham in which 29–33% had MCP rOA<sup>2</sup>. 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)<sup>1</sup>. 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

site<sup>13</sup>. The MCP joints may be an early site of hand OA, occurring prior to changes in other joints as suggested by Kalichman, *et al*<sup>33</sup>, 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)<sup>34</sup>. The literature contains many studies that examine the relationship between sCOMP and knee or hip OA<sup>9,28,34</sup>; however, there are few studies that explore this relationship in hand OA. Higher sCOMP levels correlate with radiographic knee OA progression<sup>28</sup>. 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 joints<sup>34</sup>. Levels of sCOMP are also associated with the presence of hip rOA and progression of joint space narrowing at the hip<sup>35</sup>. 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 age<sup>36</sup>. Associations have been found between sCOMP and joint space narrowing at the IP and MCP joints (inversely

associated) and MCP osteophytes<sup>13</sup>. Serum COMP, as part of a principal component, was associated with hand rOA score in the GARP cohort<sup>21</sup>. 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 alone<sup>13</sup>.

HA is a glycosaminoglycan found in many joint tissues, and is an important component of articular cartilage and synovium<sup>14</sup>. It is a marker for synovitis and joint inflammation and is influenced by a variety of factors such as food intake<sup>37</sup>, activity levels, and disease<sup>38</sup>. HA has been considered a promising biomarker for OA diagnosis and disease burden<sup>13,32,39</sup>. Higher serum levels of HA have been associated with knee KL grades<sup>40</sup>, knee and hip rOA<sup>10,41,42</sup>, an increased number of affected joints<sup>10</sup>, higher total burden of osteophytes<sup>13</sup>, and greater number of joint space narrowing faces in the MCP and CMC joints<sup>13</sup>. In the extended CARRIAGE family study, although not statistically significant, HA was higher among participants with clinically defined hand OA compared to those without<sup>36</sup>. 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 levels<sup>14</sup>. 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)<sup>43</sup> and is accepted to be a source of pain in knee OA<sup>44,45</sup>. 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.

## ACKNOWLEDGMENT

We thank the Johnston County Osteoarthritis Project staff and participants, without whom this study would not have been possible, and Dr. Ellen Roberts, University of North Carolina, Chapel Hill, for assistance with the initial abstracts through the Medical Student Training in Aging Research program.

## REFERENCES

1. Dahaghin S, Bierma-Zeinstra SM, Ginai AZ, Pols HA, Hazes JM, Koes BW. Prevalence and pattern of radiographic hand osteoarthritis and association with pain and disability (the Rotterdam study). *Ann Rheum Dis* 2005;64:682-7.
2. Zhang Y, Xu L, Nevitt MC, Niu J, Goggins JP, Aliabadi P, et al. Lower prevalence of hand osteoarthritis among Chinese subjects in Beijing compared with white subjects in the United States: the Beijing Osteoarthritis Study. *Arthritis Rheum* 2003;48:1034-40.
3. Dillon CF, Hirsch R, Rasch EK, Gu Q. Symptomatic hand osteoarthritis in the United States: prevalence and functional impairment estimates from the third U.S. National Health and Nutrition Examination Survey, 1991-1994. *Am J Phys Med Rehabil* 2007;86:12-21.
4. Kwok WY, Vliet Vlieland TP, Rosendaal FR, Huizinga TW, Kloppenburg M. Limitations in daily activities are the major determinant of reduced health-related quality of life in patients with hand osteoarthritis. *Ann Rheum Dis* 2011;70:334-6.
5. Cole A, Gill TK, Taylor AW, Hill CL. Prevalence and associations of hand pain in the community: results from a population-based study. *Scand J Rheumatol* 2011;40:145-9.
6. Slatkowsky-Christensen B, Mowinckel P, Loge JH, Kvien TK. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls, and normative data. *Arthritis Rheum* 2007;57:1404-9.
7. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. *Ann Rheum Dis* 2011;70:921-8.
8. Lee HJ, Paik NJ, Lim JY, Kim KW, Gong HS. The impact of digit-related radiographic osteoarthritis of the hand on grip-strength and upper extremity disability. *Clin Orthop Relat Res* 2012;470:2202-8.
9. Golightly YM, Marshall SW, Kraus VB, Renner JB, Villaveces A, Casteel C, et al. Biomarkers of incident radiographic knee osteoarthritis: do they vary by chronic knee symptoms? *Arthritis Rheum* 2011;63:2276-83.
10. Elliott AL, Kraus VB, Luta G, Stabler T, Renner JB, Woodard J, et al. Serum hyaluronan levels and radiographic knee and hip osteoarthritis in African Americans and Caucasians in the Johnston

- County Osteoarthritis Project. *Arthritis Rheum* 2005;52:105-11.
11. Kelman A, Lui L, Yao W, Krumme A, Nevitt M, Lane NE. Association of higher levels of serum cartilage oligomeric matrix protein and N-telopeptide crosslinks with the development of radiographic hip osteoarthritis in elderly women. *Arthritis Rheum* 2006;54:236-43.
  12. Williams FM, Spector TD. Biomarkers in osteoarthritis. *Arthritis Res Ther* 2008;10:101.
  13. Kraus VB, Kepler TB, Stabler T, Renner J, Jordan J. First qualification study of serum biomarkers as indicators of total body burden of osteoarthritis. *PLoS One* 2010;5:e9739.
  14. Filkova M, Senolt L, Braun M, Hulejova H, Pavelkova A, Sleglova O, et al. Serum hyaluronic acid as a potential marker with a predictive value for further radiographic progression of hand osteoarthritis. *Osteoarthritis Cartilage* 2009;17:1615-9.
  15. Bijsterbosch J, van Bommel JM, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TW, et al. Systemic and local factors are involved in the evolution of erosions in hand osteoarthritis. *Ann Rheum Dis* 2011;70:326-30.
  16. Silvestri T, Pulsatelli L, Dolzani P, Punzi L, Meliconi R. Analysis of cartilage biomarkers in erosive and non-erosive osteoarthritis of the hands. *Osteoarthritis Cartilage* 2004;12:843-5.
  17. Pansulaia I, Kalichman L, Kobylansky E. Association between radiographic hand osteoarthritis and RANKL, OPG and inflammatory markers. *Osteoarthritis Cartilage* 2010;18:1448-53.
  18. Bos SD, Kloppenburg M, Suchiman E, van Beelen E, Slagboom PE, Meulenbelt I. The role of plasma cytokine levels, CRP and Selenoprotein S gene variation in OA. *Osteoarthritis Cartilage* 2009;17:621-6.
  19. Punzi L, Ramonda R, Oliviero F, Sfriso P, Mussap M, Plebani M, et al. Value of C reactive protein in the assessment of erosive osteoarthritis of the hand. *Ann Rheum Dis* 2005;64:955-7.
  20. Vlad SC, Neogi T, Aliabadi P, Fontes JD, Felson DT. No association between markers of inflammation and osteoarthritis of the hands and knees. *J Rheumatol* 2011;38:1665-70.
  21. Meulenbelt I, Kloppenburg M, Kroon HM, Houwing-Duistermaat JJ, Garnero P, Hellio-Le Graverand MP, et al. Clusters of biochemical markers are associated with radiographic subtypes of osteoarthritis (OA) in subject with familial OA at multiple sites. The GARP study. *Osteoarthritis Cartilage* 2007;15:379-85.
  22. Scarpellini M, Lurati A, Vignati G, Marrazza MG, Telese F, Re K, et al. Biomarkers, type II collagen, glucosamine and chondroitin sulfate in osteoarthritis follow-up: the "Magenta osteoarthritis study". *J Orthop Traumatol* 2008;9:81-7.
  23. Jordan JM, Linder GF, Renner JB, Fryer JG. The impact of arthritis in rural populations. *Arthritis Care Res* 1995;8:242-50.
  24. Nelson AE, Chaudhary S, Kraus VB, Fang F, Chen JC, Schwartz TA, et al. Whole blood lead levels are associated with biomarkers of joint tissue metabolism in African American and white men and women: The Johnston County Osteoarthritis Project. *Environ Res* 2011;111:1208-14.
  25. Davis MA, Ettinger WH, Neuhaus JM. Obesity and osteoarthritis of the knee: evidence from the National Health and Nutrition Examination Survey (NHANES I). *Semin Arthritis Rheum* 1990;3 Suppl 1:34-41.
  26. Allen KD, DeVellis RF, Renner JB, Kraus VB, Jordan JM. Validity and factor structure of the AUSCAN Osteoarthritis Hand Index in a community-based sample. *Osteoarthritis Cartilage* 2007;15:830-6.
  27. Bellamy N, Campbell J, Haroui B, Gerez-Simon E, Buchbinder R, Hobby K, et al. Clinimetric properties of the AUSCAN Osteoarthritis Hand Index: an evaluation of reliability, validity and responsiveness. *Osteoarthritis Cartilage* 2002;10:863-9.
  28. Vilim V, Olejarova M, Machacek S, Gatterova J, Kraus VB, Pavelka K. Serum levels of cartilage oligomeric matrix protein (COMP) correlate with radiographic progression of knee osteoarthritis. *Osteoarthritis Cartilage* 2002;10:707-13.
  29. Mazzuca SA, Poole AR, Brandt KD, Katz BP, Lane KA, Lobanok T. Associations between joint space narrowing and molecular markers of collagen and proteoglycan turnover in patients with knee osteoarthritis. *J Rheumatol* 2006;33:1147-51.
  30. Kellgren JH, Lawrence JS, eds. *The epidemiology of chronic rheumatism: atlas of standard radiographs of arthritis*. Oxford: Blackwell Scientific; 1963.
  31. Kraus VB, Jordan JM, Doherty M, Wilson AG, Moskowitz R, Hochberg M, et al. The Genetics of Generalized Osteoarthritis (GOGO) study: study design and evaluation of osteoarthritis phenotypes. *Osteoarthritis Cartilage* 2007;15:120-7.
  32. van Spil WE, DeGroot J, Lems WF, Oostveen JC, Lafeber FP. Serum and urinary biochemical markers for knee and hip-osteoarthritis: a systematic review applying the consensus BIPED criteria. *Osteoarthritis Cartilage* 2010;18:605-12.
  33. Kalichman L, Cohen Z, Kobylansky E, Livshits G. Patterns of joint distribution in hand osteoarthritis: contribution of age, sex, and handedness. *Am J Hum Biol* 2004;16:125-34.
  34. Clark AG, Jordan JM, Vilim V, Renner JB, Dragomir AD, Luta G, et al. Serum cartilage oligomeric matrix protein reflects osteoarthritis presence and severity: the Johnston County Osteoarthritis Project. *Arthritis Rheum* 1999;42:2356-64.
  35. Conrozier T, Saxne T, Fan CS, Mathieu P, Tron AM, Heinegard D, 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.
  36. Chen HC, Shah S, Stabler TV, Li YJ, Kraus VB. Biomarkers associated with clinical phenotypes of hand osteoarthritis in a large multigenerational family: the CARRIAGE family study. *Osteoarthritis Cartilage* 2008;16:1054-9.
  37. Fraser JR, Gibson PR. Mechanisms by which food intake elevates circulating levels of hyaluronan in humans. *J Intern Med* 2005;258:460-6.
  38. Inoue R, Ishibashi Y, Tsuda E, Yamamoto Y, Matsuzaka M, Takahashi I, et al. Knee osteoarthritis, knee joint pain and aging in relation to increasing serum hyaluronan level in the Japanese population. *Osteoarthritis Cartilage* 2011;19:51-7.
  39. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis biomarkers: a proposed approach. *Osteoarthritis Cartilage* 2006;14:723-7.
  40. Davis CR, Karl J, Granell R, Kirwan JR, Fasham J, Johansen J, et al. Can biochemical markers serve as surrogates for imaging in knee osteoarthritis? *Arthritis Rheum* 2007;56:4038-47.
  41. Garnero P, Piperno M, Gineyts E, Christgau S, Delmas PD, Vignon E. Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. *Ann Rheum Dis* 2001;60:619-26.
  42. Sharif M, George E, Shepstone L, Knudson W, Thonar EJ, Cushnaghan J, et al. Serum hyaluronic acid level as a predictor of disease progression in osteoarthritis of the knee. *Arthritis Rheum* 1995;38:760-7.
  43. Haugen IK, Boyesen P, Slatkowsky-Christensen B, Sesseng S, van der Heijde D, Kvien TK. Associations between MRI-defined synovitis, bone marrow lesions and structural features and measures of pain and physical function in hand osteoarthritis. *Ann Rheum Dis* 2012;71:899-904.
  44. Hunter DJ, Zhang W, Conaghan PG, Hirko K, Menashe L, Li L, et al. Systematic review of the concurrent and predictive validity of MRI biomarkers in OA. *Osteoarthritis Cartilage* 2011;19:557-88.
  45. Ayril X, Pickering EH, Woodworth TG, Mackillop N, Dougados M. Synovitis: a potential predictive factor of structural progression of medial tibiofemoral knee osteoarthritis — results of a 1 year longitudinal arthroscopic study in 422 patients. *Osteoarthritis Cartilage* 2005;13:361-7.