Published in final edited form as:
Osteoarthritis Cartilage. 2008 September ; 16(9): 1054–1059. doi:10.1016/j.joca.2007.12.010.

Biomarkers Associated with Clinical Phenotypes of Hand Osteoarthritis in a Large Multigenerational Family: the CARRIAGE Family Study

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Abstract

Objective—To evaluate biological markers as potential quantitative traits of clinical osteoarthritis (OA) in a large multigenerational family in the Carolinas of the U.S. known as the CARRIAGE family.

Methods—During a series of three family reunions over 6 years, we ascertained 365 family members. We performed clinical hand examinations (n=287), and obtained sera (n=278) for seven OA-related biomarkers (PIIANP, CPII, C_2C, COMP, HA, hs-CRP and glycated serum protein). Three hand OA definitions were evaluated - clinical ACR and GOGO criteria, and any single hand joint involvement. Non-hand OA was defined as a negative hand examination for OA but varying prevalence of joint symptoms; the control group was defined as having neither symptoms nor evidence for clinical hand OA.

Results—Mean ln HA, ln COMP, and ln hs-CRP were significantly higher in the hand OA group, compared with the non-hand OA or control group. Adjusted for age and sex, mean ln PIIANP (a collagen II synthesis marker) was significantly lower in the hand OA group compared with the other groups. Among those without clinical hand OA, Glycated serum protein was associated with hand joint symptoms.

Conclusions—This is the first report, to our knowledge, showing an association of OA biomarkers and hand OA based on physical examination alone. Analyses using these biomarkers as quantitative traits could reveal novel genetic loci and facilitate exploration of the genetic susceptibility to OA.

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Keywords

Osteoarthritis; biomarkers; hand; genetics

Introduction

Osteoarthritis (OA) is the most common joint disorder causing chronic disability in the United States and worldwide [1, 2]. By the year 2030, an estimated 22% of Americans will be affected by arthritis [3]. OA is regarded as a multifactorial disorder with both environmental and genetic components [4]; however, the exact pathogenesis remains unknown. Recently, the genetic contribution to OA has been increasingly recognized and studied. To date, through whole genome-wide linkage scans, approximately 23 different loci in 14 chromosomes have been reported to link to various OA phenotypes [4, 5]. These studies used a variety of designs, including evaluation of small families of affected relatives [6–12], twins [13], and sib-pairs [14]. So far, many of these genetic loci have been specific to particular populations, suggesting that phenotypic and ethnic variability may complicate the identification of OA susceptibility genes. Considering the challenge of the phenotypic heterogeneity of OA, we exploited a highly unique extended family-based design. The CARRIAGE family is one of the most extensively pedigreed existing families in the United States comprising nine generations originating from one founder born in the 1700's in North Carolina. The ethnic origin of this family is primarily African and Native American. We posited that linkage analysis in this relatively homogeneous large family would provide greater power to identify OA susceptibility genes.

One of the goals of the CARRIAGE family study is to identify novel genes or replicate known genes associated with OA susceptibility and progression. In the health fair type setting of our family ascertainment, we could identify cases on the basis of clinical examination but not radiograph. However, the availability of OA-related biomarkers offers the prospect of powerful tools with which to quantify OA burden. We therefore chose to evaluate seven OA biomarkers to understand, prior to their use as quantitative traits of OA, their relationship to clinical OA in this particular family. Seven biomarkers were investigated in this large multigenerational family including: HA (hyaluronan), COMP (cartilage oligomeric matrix protein), PIIANP (type IIA collagen N-propeptide), CPII (type II procollagen carboxypropeptide), C_2C (neoepitope from cleavage of CII), hs-CRP (high-sensitive C-reactive protein) and GSP (glycated serum protein). Several of these markers already fulfilled OA-related criteria for two or more categories of the BIPED (Burden of disease, Investigational, Prognostic, Efficacy of therapy, and Diagnostic) classification scheme [15] as follows: these markers match the following categories: HA – B, P; COMP – D, B, P; PIIANP – B, P, D; CPII – P, E, D; C_2C – P, E, D) [16, 17]. Although six of the seven biomarkers chosen for this study have been validated previously against radiographic OA criteria, no previous study attempted to estimate the association between these biomarkers and clinical OA criteria. To our knowledge, this is the first evidence for an association of OA biomarkers and hand OA based on physical examination alone.

Methods

Study population

The CARRIAGE (CARolinas Region Interaction of Aging, Genes and Environment) family study is a prospective family-based longitudinal study of the interactions between aging, genetic susceptibility, and environmental risk on the development of several age-related and chronic diseases including OA, cardiovascular disease, and eye disease (glaucoma, and macular degeneration). The extended family described here consists of 3357 pedigreed

members dating back nine generations in the United States. Pedigree data were obtained from three sources: 1) a book detailing the genealogy of the descendents of this forefather; 2) family history questionnaires distributed by mail and completed during the family reunions; and 3) genealogy data collected by a family member. These data were combined using Progeny© software for genetic database and pedigree management. We were able to successfully document 3327 family members from the nine generations, with 2795 family members completely connected to the original founder.

Clinical Ascertainment

Ascertainment of 365 members, 18 years of age and older, was accomplished at three family reunions between 2002 and 2006 and included blood sampling (n=350), ascertainment of extensive general medical history (n=365), measurement of body mass index (n=309), self-report of joint symptoms (pain, aching, stiffness most days) of the hands, knees, hips, spine, ankles, big toe, shoulders, elbows, and wrists (n=341), and Rheumatologist-performed hand physical examinations for OA (n=278). Two participants were found to have credible evidence for a diagnosis for rheumatoid arthritis and were excluded from these analyses. Additional objective measures collected included: anthropometric data (weight, height), blood pressure, calcaneal bone mineral density using a Norland Apollo™ DEXA, ophthalmologic slit lamp examinations, and physical function testing in members 65 years of age and over. Written informed consent was obtained from each participant and the study was conducted with the approval of the Duke Institutional Review Board. All information and work was conducted under a Federal Certificate of Confidentiality to ensure the privacy of each participating member’s clinical and genetic data.

Definitions of hand OA

Hand OA was defined according to three definitions: ACR (American College of Rheumatology) criteria [18], GOGO (Genetics of Generalized OA) criteria [14], and any single hand joint involvement. We used modified ACR criteria consisting of 1) hard tissue enlargement of two or more of 10 selected joints; 2) hard tissue enlargement of two or more DIP joints; and 3) fewer than three swollen metacarpophalangeal (MCP) joints; of note, hand symptoms were not required. The GOGO criteria for determining hand OA affection status consisted of 1) a minimum of 3 joint bony enlargement (of distal or proximal interphalangeal joints - DIP and PIP) or carpometacarpal (CMC-1) squaring, and two of the three joints involving the same joint group; 2) bony enlargement of at least one DIP of digits 2–5; 3) bilateral hand involvement; 4) no more than three swollen MCPs. Any single joint involvement was defined as hard tissue enlargement of any DIP or PIP or CMC-1 squaring. Participant group status was assigned on the basis of clinical hand examination as either hand OA or non-hand OA. The non-hand OA group had symptoms (pain, aching or stiffness on most days in the last year) in at least one joint system in the body; the control group had neither clinical hand OA nor symptoms in any joint system.

Serum Biomarker Analyses

Blood samples were processed, aliquoted, and stored within 4 hours of collection at - 80°C until biomarker analyses were performed. Serum biomarker analyses were repeated as necessary for samples with a > 15% coefficient of variation (CV).

COMP (cartilage oligomeric matrix protein)—COMP was measured by an in-house ELISA method as previously described [19, 20], using monoclonal antibodies 17C10 and 16F12 against human COMP. The minimum detection limit is 120 ng/ml. Intra-assay and inter-assay CVs were < 5.8% and 8.7%, respectively.

HA (hyaluronan)—HA was measured by enzyme-linked binding protein assay (Corgenix Inc. Westminster, Colorado, USA). The assay uses enzyme-conjugated hyaluronic acid binding protein (HABP) from bovine cartilage to specifically capture HA from human serum. The minimum detection limit is established at 10 ng/ml. Intra-assay and inter-assay CVs were < 4.7% and 7.0%, respectively.

PIIANP (type IIA collagen N-propeptide)—PIIANP, a marker of a fetal form of collagen II recapitulated in OA, was measured by competitive ELISA (LINCO Research, St. Charles, MO, USA). The minimum detection limit is 17.2 ng/ml. Intra-assay and inter-assay CVs were < 6.6% and 7.8%, respectively.

CPII (type II procollagen carboxy-propeptide)—CPII, a marker of the adult form of collagen II synthesis, was measured by competitive ELISA (IBEX, Montreal, Quebec, Canada). The minimum detection limit is estimated to be 35.1 ng/ml. Intra-assay and inter-assay CVs were < 3.7% and 9.1%, respectively.

C_2C (neoepitope from cleavage of CII)—A competitive ELISA (IBEX) was used to measure the neoepitope produced by the cleavage of type II collagen (C_2C). The minimum detection limit is reported as 7.3 ng/ml. Intra-assay and inter-assay CVs are < 2.4% and 9.5%, respectively.

Hs-CRP (High-sensitivity C-reactive protein)—Hs-CRP was detected by a solid-phase sandwich ELISA (MAGIWEL; UBI, Mountain View, CA). The minimum detection limit is estimated to be 0.35 ng/ml. Intra-assay and inter-assay CVs were < 3.9% and 8.5%, respectively.

GSP (glycated serum protein)—We quantified GSP to measure non-enzymatic glycation. In contrast to hemoglobin A1c (HbA1c), which requires fresh blood for analysis, GSP can be measured in frozen sera. GSP was measured by a specific enzymatic method (DIAZYME) based on direct assessment of fructosamine in serum [21] with colorimetric detection. An assay sensitivity of 30 μmole/L is reported by the manufacturer. Intra-assay and inter-assay CVs were < 2% and <3%, respectively.

Statistical Analysis

Biomarker data were natural logarithm transformed to meet assumptions of normal distribution of the data for parametric statistical analysis, performed using GraphPad Prism (GraphPad software, San Diego, CA) and JMP (SAS, Cary, NC) software. Results were analyzed using One-way ANOVA with Tukey-Kramer multiple comparison post-hoc test. Pearson correlation was performed to evaluate for correlation among the biomarkers.

Results

All ten of the major family branches were sampled and included both descendants of the original founder and married-in members of the family. The baseline characteristics for the 341 participants with available joint symptom data are shown in Table 1. Two-thirds of the participants were women. Age and body mass index (BMI) were similar for women and men as were subjective symptoms of the hand joints. Subjective joint complaints were only dissimilar by sex for the spine and big toe.

Biomarkers and Hand Phenotypes

Six of the seven serum biomarkers analyzed were chosen on the basis of literature evidence suggesting some association with OA. To avoid potential confounding by high cartilage

turnover due to other arthropathies or by cartilage growth plate metabolism, we excluded 2 participants with rheumatoid arthritis and the 5 participants younger than 25 years of age. Seven serum biomarkers were analyzed for the 271 skeletally mature participants with available hand examination data and sera. Mean ln serum HA, COMP, and C_2C were consistently higher in the hand OA group than the non-hand OA and control groups for all definitions of hand OA (Table 2). This difference was significant for HA (all definitions), hs-CRP (all definitions) and COMP (any single hand joint involvement definition). In addition, hs-CRP was significantly higher in Hand OA and Non-Hand OA (with joint symptoms) than Controls, with the strength of the association varying by hand OA definition.

Overall, five of the seven biomarkers increased significantly with age: HA ($r=0.57$, $p<0.0001$), COMP ($r=0.33$, $p< 0.0001$), PIIANP ($r=0.20$, $p=0.0011$), C_2C ($r=0.16$, $p=0.0016$), and hs-CRP ($r=0.12$, $p=0.048$). When adjusted for age and sex, the collagen synthesis marker, PIIANP, was significantly lower in the Hand OA group compared with the Control group for all definitions of hand OA. After age and gender adjustment, the difference in HA among groups was marginally significant (ANOVA $p=0.08$). The age and gender adjusted ratio of HA/PIIANP reflected a significant excess of cartilage degradation over synthesis in the Hand OA group and Non-hand OA (with joint symptoms) group compared with Control (Table 3).

Biomarkers and hand symptoms

A total of 120 participants reported joint symptoms in the hand or in another joint system but did not meet the definition of clinical hand OA based on even the least stringent criterion (any single joint involvement). This group was further subdivided into those with hand symptoms +/− symptoms elsewhere (Group A), and those without hand symptoms but with symptoms outside the hand (Group B). We compared these two groups with Controls (Group C) to discern potential biomarkers of early OA. Ln GSP was significantly higher in those with hand symptoms compared with Controls (Figure 1). After adjustment for diabetes history, ln GSP was significantly higher in those with hand symptoms compared with controls ($p=0.039$). Ln HA, and the ratio of HA to collagen synthesis (HA/PIIANP) was significantly higher in those with symptoms outside the hand (Group B) compared with Controls.

Correlations Among the Biomarkers

All of the biomarkers, except hs-CRP, correlated with HA (Table 4). There was a significant correlation between COMP and glycated protein. Not surprisingly, there were strong correlations among the type II collagen biomarkers (PIIANP, CPII, and C2C).

Discussion

We have been able to ascertain multiple members of a large extended family for the purposes of evaluating aging, environmental and genetic risk for OA. Most previous studies of biomarkers and OA were focused on knees and hips and have relied on radiographs. However, compared with knee or hip OA, hand OA is easier to evaluate by physical examination and has been reported to display stronger concordance and familial aggregation. The reunion venues at which these individuals were assessed afforded the possibility of blood collection and limited musculoskeletal examinations, but not radiographic assessment. Based on the strength of past radiographic validation of a number of OA-related biomarkers, we hypothesized that biomarkers could be used as quantitative traits of OA. Our goal therefore, in this study, was to evaluate the strength of association of known OA-related biomarkers to the clinical OA data available in this family.

The ethnic composition of this family is a unique mixture of mainly African and Native American. With a few exceptions [20, 22], the majority of OA biomarker validation studies have been performed in Caucasians. This study is therefore novel for specifically evaluating the strength of association between the clinical OA phenotypes and OA-related biomarkers in a non-Caucasian family. This study demonstrated the feasibility of this goal in that we identified four biomarkers, HA, COMP, PIIANP and GSP, that were associated with hand OA in this family on the basis of clinical examination or hand symptoms. To our knowledge, this is the first report of an association of OA-related biomarkers and hand OA based upon physical examination data alone.

We observed lower PIIANP values in association with hand OA. Although Sharif et al reported that serum PIIANP was higher in knee OA progressors compared with non-progressors, his was a community-based cohort with relatively mild knee OA [23]; most of the previous studies have demonstrated that serum PIIANP was decreased in patients with knee OA compared to controls [24–26].

We observed an increase in HA and COMP in association with hand OA. In the Johnston County Osteoarthritis biomarkers sub-studies, serum COMP and HA increased significantly with knee and hip OA, even after adjustment for other risk factors including age [19, 20]. The association of serum HA and COMP with hand OA in our cohort was not independent of age. These results may partially arise from the direct comparison of highly sensitive biomarkers with only moderately sensitive physical examination criteria without any supporting radiographs.

Joint symptoms in the absence of clinical examination findings may be an indicator of early OA. We observed higher levels of hs-CRP and GSP in the group with hand symptoms but no hand OA by physical examination. Thus, our data suggest that hs-CRP and GSP may be biomarkers of early sub-clinical hand OA; this possibility has been suggested by several other studies of hs-CRP [27, 28]. We assessed GSP as an intermediate to advanced glycation end product (AGE) formation. AGE are formed by non-enzymatic reactions in the process of post-translational modification, have been involved in the aging process and the pathogenesis of several diseases, including rheumatoid arthritis (RA) and diabetes. A recent study has showed accumulation of AGEs is a potential risk factor for OA [29]. Verzijl N et al also showed that AGE crosslinking may result in pathologic stiffness of cartilage *in vitro* [30]. Senolt et al reported an increased serum concentration of pentosidine, a form of AGE, in patients with knee OA. In addition, he found a significant correlation between synovial fluid COMP and serum pentosidine (R^2=0.11, $p<0.05$) [31]. In our study, serum glycated protein was correlated with serum COMP (R^2=0.26, $p<0.0001$) along with HA (R^2=0.14, $p<0.0001$). A larger sample size, or more sensitive phenotyping methods, may be required to see an association between GSP and OA.

A potential limitation of this study was the inability to conduct radiographic phenotyping due to the health fair type setting of the ascertainment venues. We also have knee examination data on only 120 individuals as this aspect of the study was only added in 2006. Therefore, this, as other studies, could be confounded by cartilage degradation at other joint sites for which clinical examination data were unavailable. Nevertheless, we have self-reported arthritis symptoms on all participants for all joint sites. Moreover, our study was community-based and therefore not selected for OA. In this way, it is potentially more representative of the population at large although healthier family members were probably more likely to participate.

In summary, we report the first evidence for an association of OA biomarkers and clinical hand OA. Several of the biological markers (HA, COMP, PIIANP, hs-CRP, GSP, and HA/

PIIANP) evaluated in this large family showed an association with clinical phenotypes of hand OA or hand symptoms. This study design offers the prospect of minimizing genetic heterogeneity through the analysis of a large family, and demonstrates the feasibility of utilizing several OA-related biomarkers as quantitative traits to identify underlying OA genes in this family.

Acknowledgments

We would like to extend our thanks to Dr. William Kraus for funding assistance, to Dr. Vladimir Vilim for the kind gift of the 16F12/17C10 monoclonal antibodies, to Norine Hall, Carol Haynes, and Sarah Nelson for database management, and everyone who made the reunions possible.

Funding: NIH/NIA Claude D. Pepper OAIC 2P60 AG11268, the Mary Duke Biddle Foundation, the Trent Foundation, and a student grant from the Taiwanese government. Support for biomarker analyses was also provided by NIH/NIA Claude D. Pepper OAIC P30 AG028716-03.

References

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, et al. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. Arthritis Rheum. 1998; 41:778–799. [PubMed: 9588729]
2. Hogue JH, Mersfelder TL. Pathophysiology and first-line treatment of osteoarthritis. Ann Pharmacother. 2002; 36:679–686. [PubMed: 11918520]
3. Elders MJ. The increasing impact of arthritis on public health. J Rheumatol Suppl. 2000; 60:6–8. [PubMed: 11032095]
4. Peach CA, Carr AJ, Loughlin J. Recent advances in the genetic investigation of osteoarthritis. Trends Mol Med. 2005; 11:186–191. [PubMed: 15823757]
5. Jordan JM, Kraus VB, Hochberg MC. Genetics of osteoarthritis. Curr Rheumatol Rep. 2004; 6:7–13. [PubMed: 14713397]
6. Chapman K, Mustafa Z, Irven C, Carr AJ, Clipsham K, Smith A, et al. Osteoarthritis-susceptibility locus on chromosome 11q, detected by linkage. Am J Hum Genet. 1999; 65:167–174. [PubMed: 10364529]
7. Loughlin J, Mustafa Z, Irven C, Smith A, Carr AJ, Sykes B, et al. Stratification analysis of an osteoarthritis genome screen-suggestive linkage to chromosomes 4, 6, and 16. Am J Hum Genet. 1999; 65:1795–1798. [PubMed: 10577938]
8. Leppavuori J, Kujala U, Kinnunen J, Kaprio J, Nissila M, Heliovaara M, et al. Genome scan for predisposing loci for distal interphalangeal joint osteoarthritis: evidence for a locus on 2q. Am J Hum Genet. 1999; 65:1060–1067. [PubMed: 10486325]
9. Stefansson SE, Jonsson H, Ingvarsson T, Manolescu I, Jonsson HH, Olafsdottir G, et al. Genomewide scan for hand osteoarthritis: a novel mutation in matrilin-3. Am J Hum Genet. 2003; 72:1448–1459. [PubMed: 12736871]
10. Demissie S, Cupples LA, Myers R, Aliabadi P, Levy D, Felson DT. Genome scan for quantity of hand osteoarthritis: the Framingham Study. Arthritis Rheum. 2002; 46:946–952. [PubMed: 11953971]
11. Greig C, Spreckley K, Aspinwall R, Gillaspy E, Grant M, Ollier W, et al. Linkage to nodal osteoarthritis: quantitative and qualitative analyses of data from a whole-genome screen identify trait-dependent susceptibility loci. Ann Rheum Dis. 2006; 65:1131–1138. [PubMed: 16504993]
12. Hunter DJ, Demissie S, Cupples LA, Aliabadi P, Felson DT. A genome scan for joint-specific hand osteoarthritis susceptibility: The Framingham Study. Arthritis Rheum. 2004; 50:2489–2496. [PubMed: 15334462]
13. Livshits G, Kato BS, Zhai G, Hart DJ, Hunter D, MacGregor AJ, et al. Genomewide linkage scan of hand osteoarthritis in female twin pairs showing replication of quantitative trait loci on chromosomes 2 and 19. Ann Rheum Dis. 2007; 66:623–627. [PubMed: 17127684]

14. 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; 15:120–127. [PubMed: 17113325]
15. Bauer DC, Hunter DJ, Abramson SB, Attur M, Corr M, Felson D, et al. Classification of osteoarthritis biomarkers: a proposed approach. Osteoarthritis Cartilage. 2006; 14:723–727. [PubMed: 16733093]
16. Rousseau JC, Delmas PD. Biological markers in osteoarthritis. Nat Clin Pract Rheumatol. 2007; 3:346–356. [PubMed: 17538566]
17. Charni-Ben Tabassi N, Garnero P. Monitoring cartilage turnover. Curr Rheumatol Rep. 2007; 9:16–24. [PubMed: 17437662]
18. Altman RD, Fries JF, Bloch DA, Carstens J, Cooke TD, Genant H, et al. Radiographic assessment of progression in osteoarthritis. Arthritis Rheum. 1987; 30:1214–1225. [PubMed: 3689459]
19. 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; 10:707–713. [PubMed: 12202123]
20. 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; 52:105–111. [PubMed: 15641044]
21. Wang Y, Dou C, Yuan C, Datta A. Development of an automated enzymatic assay for the determination of glycated serum protein in human serum. Clin Chem. 2005; 51:1991–1992. [PubMed: 16299899]
22. Jordan JM, Luta G, Stabler T, Renner JB, Dragomir AD, Vilim V, et al. Ethnic and sex differences in serum levels of cartilage oligomeric matrix protein: the Johnston County Osteoarthritis Project. Arthritis Rheum. 2003; 48:675–681. [PubMed: 12632420]
23. Sharif M, Kirwan J, Charni N, Sandell LJ, Whittles C, Garnero P. A 5-yr longitudinal study of type IIA collagen synthesis and total type II collagen degradation in patients with knee osteoarthritis--association with disease progression. Rheumatology (Oxford). 2007; 46:938–943. [PubMed: 17387119]
24. Rousseau JC, Sandell LJ, Delmas PD, Garnero P. Development and clinical application in arthritis of a new immunoassay for serum type IIA procollagen NH2 propeptide. Methods Mol Med. 2004; 101:25–37. [PubMed: 15299208]
25. Rousseau JC, Zhu Y, Miossec P, Vignon E, Sandell LJ, Garnero P, et al. Serum levels of type IIA procollagen amino terminal propeptide (PIIANP) are decreased in patients with knee osteoarthritis and rheumatoid arthritis. Osteoarthritis Cartilage. 2004; 12:440–447. [PubMed: 15135140]
26. Garnero P, Ayral X, Rousseau JC, Christgau S, Sandell LJ, Dougados M, et al. Uncoupling of type II collagen synthesis and degradation predicts progression of joint damage in patients with knee osteoarthritis. Arthritis Rheum. 2002; 46:2613–2624. [PubMed: 12384919]
27. Sturmer T, Brenner H, Koenig W, Gunther KP. Severity and extent of osteoarthritis and low grade systemic inflammation as assessed by high sensitivity C reactive protein. Ann Rheum Dis. 2004; 63:200–205. [PubMed: 14722211]
28. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum. 1997; 40:723–727. [PubMed: 9125256]
29. DeGroot J, Verzijl N, Wenting-van Wijk MJ, Jacobs KM, Van El B, Van Roermund PM, et al. Accumulation of advanced glycation end products as a molecular mechanism for aging as a risk factor in osteoarthritis. Arthritis Rheum. 2004; 50:1207–1215. [PubMed: 15077303]
30. Verzijl N, DeGroot J, Ben ZC, Brau-Benjamin O, Maroudas A, Bank RA, et al. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: a possible mechanism through which age is a risk factor for osteoarthritis. Arthritis Rheum. 2002; 46:114–123. [PubMed: 11822407]
31. Senolt L, Braun M, Olejarova M, Forejtova S, Gatterova J, Pavelka K. Increased pentosidine, an advanced glycation end product, in serum and synovial fluid from patients with knee osteoarthritis and its relation with cartilage oligomeric matrix protein. Ann Rheum Dis. 2005; 64:886–890. [PubMed: 15897309]

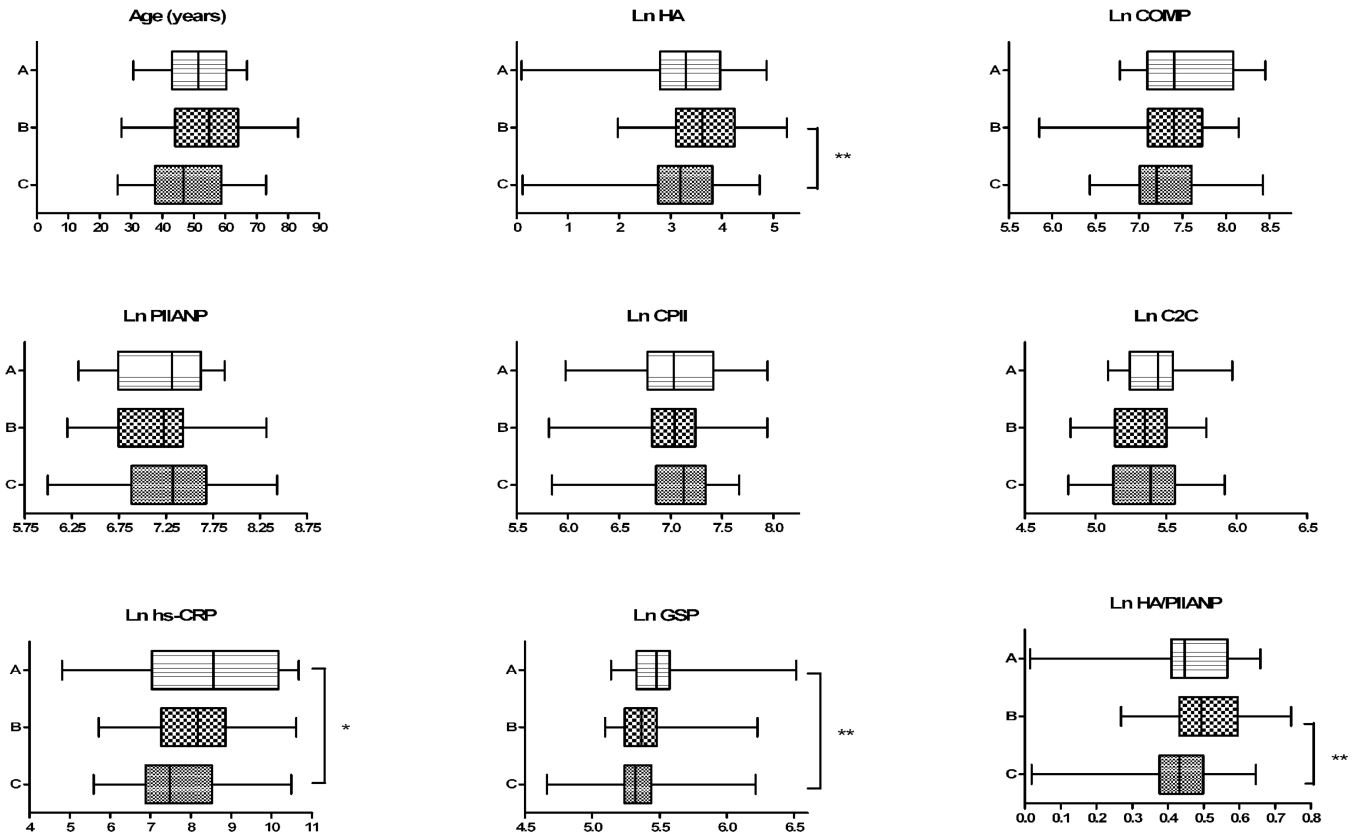

Figure 1. Biomarkers and hand symptoms

The individuals without clinical hand OA (on the basis of a negative hand joint examination) were categorized into 3 groups: Group A (n=18) - no hand OA by examination, presence of hand symptoms, and possible symptoms in other joint systems; Group B (n=57) - no hand OA by examination, no hand symptoms, but joint symptoms in one or more other joint systems; Group C (n=45) - no hand OA by examination, no hand symptoms, and no other joint symptoms. Box plots depict mean, 25th and 75th percentiles, and minimum and maximum. *p<0.1, **p<0.05

Table 1

Demographic characteristic of the 341 participants with joint symptom data

Characteristic	Female (n=229)	Male(n=112)
Age, mean ± SD (range), years	54.87±15.69 (18~92)	53.31±15.14 (17~85)
BMI, mean ± SD (range), kg/m^2	30.60±6.69 (18.80~60.30) (n=205)	30.90±5.98 (19.90~52.00) (n=104)
Subjective joint complaints		
Hand symptoms	36 (15.7%)	15 (13.4%)
Knee symptoms	69 (30.1%)	42 (37.5%)
Hip symptoms	39 (17.0%)	12 (10.7%)
Spine symptoms	98 (42.8%)	32 (28.6%)
Ankle symptoms	35 (15.3%)	12 (10.7%)
Shoulder symptoms	66 (28.8%)	23 (20.5%)
Elbow symptoms	20 (8.7%)	7 (6.3%)
Big toe symptoms	18 (7.9%)	1 (0.9%)

Table 2

Hand OA and biomarkers (unadjusted)

	Hand OA	Non-Hand OA	Controls
Modified hand ACR criteria	N = 36	N = 190	N = 45
Ln HA	4.18 ± 0.87 **++	3.57 ± 0.89 **	3.07 ± 1.04
Ln COMP	7.51 ± 0.41 *	7.43 ± 0.45	7.30 ± 0.48
Ln PIIANP	7.20 ± 0.54	7.10 ± 0.50 *	7.29 ± 0.53
Ln CPII	7.17 ± 0.38	7.03 ± 0.41	7.06 ± 0.43
Ln C2C	5.39 ± 0.22	5.36 ± 0.26	5.35 ± 0.28
Ln hs-CRP	8.26 ± 1.45	8.28 ± 1.44 **	7.68 ± 1.16
Ln GSP	5.44 ± 0.22	5.42 ± 0.25 *	5.34 ± 0.21
Age, years	67.7 ± 12.0 **++	55.9 ± 13.8 **	48.3 ± 12.8
GoGo hand criteria	N = 41	N = 185	N = 45
Ln HA	4.09 ± 0.86 **++	3.56 ± 0.90 **	3.07 ± 1.04
Ln COMP	7.51 ± 0.38 *	7.42 ± 0.45	7.30 ± 0.48
Ln PIIANP	7.15 ± 0.53	7.10 ± 0.50 *	7.29 ± 0.53
Ln CPII	7.10 ± 0.38	7.04 ± 0.41	7.06 ± 0.43
Ln C2C	5.40 ± 0.23	5.36 ± 0.26	5.35 ± 0.28
Ln hs-CRP	8.23 ± 1.44	8.29 ± 1.44 **	7.68 ± 1.16
Ln GSP	5.41 ± 0.22	5.43 ± 0.26 *	5.34 ± 0.21
Age, years	67.1 ± 12.2 **++	55.6 ± 13.9 **	48.3 ± 12.8
Any single hand joint involvement	N = 108	N = 118	N = 45
Ln HA	3.87 ± 0.84 **++	3.49 ± 0.94 **	3.07 ± 1.04
Ln COMP	7.50 ± 0.41 **	7.38 ± 0.46	7.30 ± 0.48
Ln PIIANP	7.09 ± 0.50 *	7.14 ± 0.52	7.29 ± 0.53
Ln CPII	7.07 ± 0.43	7.03 ± 0.39	7.06 ± 0.43
Ln C2C	5.38 ± 0.26	5.35 ± 0.26	5.35 ± 0.28
Ln hs-CRP	8.32 ± 1.54 **	8.24 ± 1.35 *	7.68 ± 1.16
Ln GSP	5.43 ± 0.25	5.43 ± 0.24 *	5.34 ± 0.21
Age, years	63.7 ± 12.1 **++	52.3 ± 13.9 **	48.3 ± 12.8

Values are mean ± SD,

* p<0.1 and

** p<0.05 comparing Hand OA or Non-hand OA with Controls;

++ p<0.05 comparing Hand OA and Non-hand OA.

HA = hyaluronan, COMP = cartilage oligomeric matrix protein, PIIANP = type IIA collagen N-propeptide, CPII = type II procollagen carboxy-propeptide, C_2C = neoepitope from cleavage of CII, hs-CRP = high-sensitivity C-reactive protein, GSP = glycated serum protein.

Osteoarthritis Cartilage. Author manuscript; available in PMC 2012 May 19.

Table 3

Hand OA and Biomarkers (mean values adjusted for age and/or gender)

	Hand OA	Non-Hand OA	Controls	P value (adjusted for age)	Hand OA	Non-Hand OA	Controls	P value (adjusted for age and gender)
Modified hand ACR criteria	N = 36	N = 190	N = 45		N = 36	N = 190	N = 45	
Ln HA	3.77 ± 0.82	3.58 ± 0.78	3.36 ± 0.80	0.08	3.79 ± 0.84	3.60 ± 0.89	3.37 ± 0.84	0.08
Ln PIIANP	7.10 ± 0.52	7.10 ± 0.50	7.36 ± 0.51	0.01	7.04 ± 0.54	7.06 ± 0.56	7.31 ± 0.53	0.01
Ln HA/PIIANP	0.53 ± 0.12	0.50 ± 0.11	0.45 ± 0.12	0.01	0.53 ± 0.12	0.51 ± 0.13	0.45 ± 0.12	0.01
GoGo hand criteria	N = 41	N = 185	N = 45		N = 41	N = 185	N = 45	
Ln HA	3.70 ± 0.82	3.59 ± 0.77	3.36 ± 0.80	0.1	3.71 ± 0.86	3.61 ± 0.88	3.38 ± 0.84	0.1
Ln PIIANP	7.04 ± 0.52	7.11 ± 0.49	7.36 ± 0.51	0.01	6.99 ± 0.54	7.07 ± 0.56	7.31 ± 0.53	0.01
Ln HA/PIIANP	0.52 ± 0.12	0.50 ± 0.11	0.45 ± 0.12	0.02	0.53 ± 0.12	0.51 ± 0.13	0.46 ± 0.12	0.02
Any single hand joint involvement	N = 108	N = 118	N = 45		N = 108	N = 118	N = 45	
Ln HA	3.59 ± 0.83	3.63 ± 0.83	3.37 ± 0.81	0.2	3.60 ± 0.90	3.64 ± 0.87	3.39 ± 0.84	0.2
Ln PIIANP	7.01 ± 0.53	7.18 ± 0.53	7.37 ± 0.51	0.0006	6.97 ± 0.56	7.14 ± 0.54	7.32 ± 0.53	0.0007
Ln HA/PIIANP	0.51 ± 0.12	0.50 ± 0.12	0.46 ± 0.12	0.02	0.52 ± 0.13	0.51 ± 0.12	0.46 ± 0.12	0.02

Values are mean ± SD

Table 4

Correlations among the serum biomarkers

Biomarkers	Ln HA	Ln COMP	Ln C2C	Ln CPII	Ln PIIANP	Ln hs-CRP
Ln COMP	0.3498***					
Ln C2C	0.2611***	0.0858				
Ln CPII	0.2154***	0.0904	0.4434***			
Ln PIIANP	0.1976***	0.0685	0.3071***	0.2984***		
Ln hs-CRP	0.0819	0.0472	−0.0575	−0.0528	0.0959*	
Ln GSP	0.1445**	0.2638***	−0.0344	0.0254	0.0369	0.0454

Correlation coefficients were determined by Pearson correlation;

* p< 0.05,

** p< 0.01,

*** P<0.0001

HA = hyaluronan, COMP = cartilage oligomeric matrix protein, PIIANP = type IIA collagen N-propeptide, CPII = type II procollagen carboxy-propeptide, C_2C = neoepitope from cleavage of CII, hs-CRP = high-sensitivity C-reactive protein, GSP = glycated serum protein.