No Association Between Markers of Inflammation and Osteoarthritis of the Hands and Knees

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ABSTRACT. ***Objective.*** Local inflammation plays a prominent role in osteoarthritis (OA). This could be reflected in the presence of elevated soluble inflammatory markers. We conducted analyses to assess the association of inflammatory markers with radiographic OA of the hands and knees in a large community-based cohort.

Methods. The Framingham Offspring cohort consists of the adult children of the original cohort and their spouses. In 1998-2001 these subjects provided blood specimens that were tested for 17 markers of systemic inflammation. In 2002-2005 these subjects had radiographs of both knees and hands. Each hand and knee joint was assigned a Kellgren and Lawrence (KL) score (0–4). We used logistic regression with generalized estimating equations and adjustment for age, sex, and body mass index to examine the association between each inflammatory marker and the presence of radiographic OA (ROA = KL grade ≥ 2) in any joint. We also constructed models for hand joints and knee joints alone.

Results. Radiographs and measures of inflammation were done for 1235 subjects (56% women, mean age 65 yrs). Of that group, 729 subjects (59%) had ROA in ≥ 1 hand or knee joint: 179 (14.3%) had knee OA, and 694 (56.2%) had hand OA. There were no significant associations between any marker of inflammation and ROA.

Conclusion. In this large sample, in which OA was carefully assessed and multiple markers measured, we found no evidence of an association between any inflammatory marker and the presence of radiographic OA. (First Release May 15 2011; J Rheumatol 2011;38:1665–70; doi:10.3899/jrheum.100971)

Key Indexing Terms:
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Osteoarthritis (OA), the prototypical "noninflammatory" arthropathy, is now well recognized to involve an inflammatory component[1]. Inflammatory cytokines produced by the synovium and chondrocytes, including interleukin 1ß (IL-1ß), tumor necrosis factor-α (TNF-α), IL-6, and others, appear to play pivotal roles in cartilage destruction. These cytokines are produced by the synovium and chondrocytes and are expressed there and in the synovial fluid[2,3].

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Some studies suggest that this local inflammation may be reflected systemically. This has been best studied with high-sensitivity C-reactive protein (CRP) serving as a marker for systemic inflammation, with several studies showing a relationship between serum CRP levels and OA of the knee[4,5,6], hip[6,7], and hands[8]. Others have found serum CRP to reflect local evidence of joint inflammation[9] or pain associated with OA[10]. Other studies, however, have reported no association of CRP with OA, especially after adjustment for the influence of body mass[10,11,12,13].

It is possible that CRP is not an optimal marker for inflammation in OA; other putative markers have been associated with some OA phenotypes. These include IL-6[14,15], TNF-α[15], TNF-receptor II (TNF-RII)[14], IL-1[16], intercellular adhesion molecule 1 (ICAM-1)[17], and adiponectin[18].

Given the local role of inflammatory cytokines in OA and the potential trafficking of inflammatory cells through OA synovium and back out into the circulation[2], there is reason to believe that some systemic inflammatory markers may be present at higher or lower than normal levels in the blood of subjects with OA, and it is possible that some of these may correlate with specific OA phenotypes. An absence of associations might suggest that inflammation is a very localized phenomenon without significant systemic effects. We examined whether elevations in some inflammatory markers known to be associated with OA, and others not yet clearly

associated with OA, were associated with radiographic OA (ROA) of the hands and/or knees in a large population-based cohort. We hypothesized that some of these markers (e.g., CRP) would be elevated in those with hand and/or knee OA.

MATERIALS AND METHODS

We used data from the Framingham Offspring Cohort. This community-based cohort consists of the adult children of members of the original Framingham Heart Study, as well as the spouses of these children. The study began in 1971 and has now completed 8 examination cycles, which take place every 4 years. Details of the selection and design have been described[19].

During the seventh examination cycle (1998-2001), as part of a study of inflammatory markers and heart disease, blood samples were collected from subjects. Standardized assays were used to measure serum markers of inflammation that could be associated with coronary heart disease; we examined their possible relevance to OA. These markers included adiponectin, plasma CD40 ligand, serum CD40 ligand, CRP, fibrinogen, ICAM-1, IL-6, lipoprotein-associated phospholipase A_2 (LP-PLA_2) activity and mass, monocyte chemoattractant protein 1 (MCP-1), myeloperoxidase (MPO), osteoprotegerin (OPG), P-selectin, resistin, TNF-α, and TNF-RII. Urine was also collected and assays were conducted to measure urine isoprostane levels corrected for the level of urine creatinine. In the case of outliers, sources of laboratory error were investigated and if none were found, the outlier was retained in the data. Erroneous values, values below the detectable limits of the assays, or missing data due to inadequate sample size were characterized as missing. Details of the assays, including intraassay coefficients of variation, have been published[20].

In 1992-95, a subset of the Framingham Offspring cohort was invited to participate in a study of OA, the Framingham Osteoarthritis Study. At callback examinations from 2002 to 2005, a sample of 1235 of these participants underwent standardized, weight-bearing, fixed-flexion radiographs of the knees and standardized posteroanterior radiographs of the hands. These protocols have been described[21,22]. Subjects with a history of inflammatory joint disease were excluded. All radiographs were read by a single academically based musculoskeletal radiologist and each hand and knee joint was assigned a Kellgren and Lawrence (KL) score from 0 to 4: 0 = no osteophytes or joint space narrowing, 1 = possible osteophytes, 2 = definite osteophytes and possible joint space narrowing, 3 = moderate osteophytes and definite joint space narrowing, and 4 = large osteophytes, severe joint space narrowing, and/or bony sclerosis[23]. The intraobserver weighted κ were 0.77 for hand KL grade, and 0.91 for knee KL grade. We defined the presence of ROA as any KL score ≥ 2.

Age and body mass index (BMI) were obtained at the same visits at which radiographs were obtained.

Analysis. All inflammatory marker measurements were standardized by dividing values by the respective SD for the relevant assay so as to allow comparisons between different markers. Therefore, OR represents the increase in the odds of ROA for a 1 SD increase in the inflammatory marker. A number of models were constructed to assess the relationship between an inflammatory marker and ROA. In each case crude models and those adjusted for age, sex, and BMI were constructed. Interaction between each marker and age, sex, and BMI were explored; the number of potential interactions found were consistent with chance, given the number of tests performed, and thus are not reported. Therefore the models without interaction are reported.

The first set of models used a joint-centered definition of ROA. We used logistic regression with generalized estimating equations (GEE) to account for multiple joints within a subject. Models were created with the inflammatory marker as the independent variable and the presence of ROA in any joint (knees or hands) as the dependent variable. The models were also repeated using only hand or only knee joints as the dependent variables.

We constructed a second set of models using subject-centered definitions of ROA to find evidence of associations between the inflammatory markers and specific, more severe OA phenotypes, where inflammation might be more likely to play a role. Again using logistic regression (without GEE), the inflammatory marker was the independent variable, while "presence of OA" in a subject was the dependent variable. In these models, we tested several different definitions of "presence of OA": (1) the presence of ROA in both thumb bases; (2) the presence of ROA in 4 or more distal interphalangeal (DIP) joints (including the first IP joint) of each hand; (3) the presence of ROA in 4 or more proximal interphalangeal (PIP) joints (including the first IP joint) of each hand; (4) the presence of ROA in 4 or more metacarpophalangeal (MCP) joints of each hand; and (5) the presence of ROA in both knees.

For a third set of models, we used the total joint load, i.e., the number of joints affected, as the outcome variable. For these models, we used linear regression with the total number of affected joints as the outcome variable. As the number of joints affected was not normally distributed, we repeated the analysis using the natural logarithm of the number of joints as the outcome. We also modeled higher-ordered relationships (square of the marker and square root of the marker).

We then explored the possibility that OA could be the cause of changes in inflammatory marker levels. We created linear models where the total number of joints affected by ROA served as the independent variable and the logarithm of the standardized inflammatory marker served as the outcome variable. The ß-coefficients in these models reflect the expected increase in the marker (in standard deviations) for each additional joint affected by ROA. Models were created with and without adjustment for age, sex, and BMI. Linear models alone were thought to be sufficient as visual inspection of the primary data (logarithm of marker vs total number of joints) and residual plots did not suggest nonlinear relationships. Plots and analyses using LOESS regression also did not suggest more complex relationships.

Finally, as inflammation could be more strongly associated with painful OA rather than ROA, we performed sensitivity analyses in which we redefined the "presence of OA" to require pain in the affected hand or knee, as well as radiographic evidence of OA (KL ≥ 2).

RESULTS

The study sample consisted of 1235 people, of whom 689 (56%) were women (Table 1). The mean age was 65.3 years (SD 9.1, median 65); 897 subjects (73%) were age 60 years or older. The mean BMI was 28.6 (SD 5.5, median 28.0). Not all subjects had assays for each inflammatory marker.

There were 729 subjects (59%) who met our definition of ROA in ≥ 1 joint: 413 women (60%) and 316 men (58%). Using our definitions, 317 subjects (26%) had thumb base OA, 76 (6%) had DIP joint OA, 28 (2%) had PIP OA, and 15 (1%) had MCP OA. There were 89 (7%) with bilateral knee

Table 1. Demographic data of the cohort and details of radiographic osteoarthritis (ROA) cases.

Characteristics	Mean (SD) or n (%)
Age, yrs	65.3 (± 9.1)
Body mass index	28.6 (± 5.5)
Women	689 (56)
Any radiographic OA (KL > 2 in any joint)	729 (59)
Men	316 (58)
Women	413 (60)
Thumb base OA (KL ≥ 2 in both hands)	317 (26)
DIP OA (KL ≥ 2 in 4 DIP joints of each hand)	76 (6)
PIP OA (KL ≥ 2 in 4 PIP joints of each hand)	28 (2)
MCP OA (KL ≥ 2 in 4 MCP joints of each hand)	15 (1)
Knee OA (KL ≥ 2 in both knees)	89 (7)

KL: Kellgren and Lawrence grade; DIP: distal interphalangeal; PIP: proximal interphalangeal; MCP: metacarpophalangeal.

OA. In measuring pain, we found that 114 subjects (9.%) had painful thumb base OA, 44 (4%) had painful DIP OA, 16 (1%) had painful PIP OA, and 3 (0.2%) had painful MCP OA. Forty-six (4%) had painful bilateral knee OA.

The joint-centered logistic regression models failed to demonstrate convincing associations between any of the inflammatory markers and ROA (Table 2). A marginal association was seen for serum CD40.

The patient-centered models also failed to find any convincing association between any of the markers and our ROA definitions (Table 3). Although some statistically significant associations were observed, these tended to be small, with 95% CI barely excluding unity. Other associations showed contradictory effects; for example, IL-6 was associated with both a higher and lower risk of OA, depending on the OA phenotype assessed. Of note, CRP was associated with a lower risk of OA in the DIP joints.

Neither linear regression model revealed an association between any marker and the total "load" of ROA (Table 4). Higher-order models suggested that 5 markers might have a relationship with the joint load. Four of these were of questionable significance [square root of TNF-RII (ß-coefficient = 0.28, p = 0.06); OPG squared (ß-coefficient = 0.07, p = 0.04); square root of MPO (ß-coefficient = 0.30, p = 0.04); and LP-PLA_2 mass squared (ß-coefficient = –0.015, p = 0.04)]. Another marker (serum CD40) was slightly more suggestive, with the ß-coefficient for the square root = 0.30, p = 0.03. However, given the large number of comparisons, none of these relationships can be said to show a definitive relationship with the total joint load.

Table 2. Joint-specific OR of radiographic osteoarthritis (ROA) for each marker. OR data are of OA in any joint, using logistic regression and accounting for multiple correlations between joints with generalized estimating equations; adjusted for age, sex, and body mass index.

Marker	N in Analysis (Maximum n = 1235)	OR of ROA for 1 SD Increase of Marker (95% CI)
Adiponectin	885	1.02 (0.91–1.14)
CD40 (serum)	1211	1.10 (1.00–1.18)
CD40 (plasma)	1229	0.99 (0.91–1.08)
C-reactive protein	1226	0.98 (0.89–1.07)
Fibrinogen	1227	0.94 (0.85–1.03)
ICAM-1	1226	1.00 (0.92–1.08)
Interleukin 6	1225	0.97 (0.89–1.05)
Isoprostanes	964	1.01 (0.91–1.13)
LP-PLA_2 activity	1227	0.95 (0.86–1.06)
LP-PLA_2 mass	1227	0.95 (0.87–1.04)
MCP1	1208	1.01 (0.95–1.07)
Myeloperoxidase	1182	1.06 (0.99–1.15)
Osteoprotegerin	1227	0.99 (0.90–1.09)
P-selectin	1229	0.97 (0.89–1.05)
Resistin	876	0.98 (0.88–1.08)
TNF-α	877	0.97 (0.91–1.04)
TNF-RII	1194	1.04 (0.95–1.13)

CD40: CD40 ligand; ICAM-1: intercellular adhesion molecule 1; isoprostanes: (urinary creatinine)/(8epi-PGF2a); LP-PLA_2: lipoprotein-associated phospholipase A_2; MCP1: monocyte chemoattractant protein; TNF-α: tumor necrosis factor-α; TNF-RII: type II TNF receptor.

Linear regression models in which the affected joint count served as the independent variable and the logarithm of the standardized marker level served as the outcome also failed to show any convincing relationship (Table 5). Although some nominally statistically significant outcomes occurred, these effects were small, and given the number of associations tested, likely occurred by chance.

In the sensitivity analysis, using symptomatic OA as the primary outcome, we again generally failed to find concrete evidence of a relationship between any inflammatory marker and OA (results not shown). However, relatively strong associations of potential interest include fibrinogen with DIP OA (OR 0.65, 95% CI 0.45, 0.95); IL-6 with DIP OA (OR 0.31, 95% CI 0.12, 0.77); LP-PLA_2 activity with PIP OA (OR 1.8, 95% CI 1.1, 3.0); and LP-PLA_2 mass with PIP OA (OR 2.0, 95% CI 1.3, 3.1).

DISCUSSION

We failed to find convincing evidence of a cross-sectional relationship between any systemic inflammatory marker and ROA. Despite a number of studies suggesting a relationship between serum CRP levels and OA, we could not reproduce this finding in this community-based sample. Nor did we demonstrate a convincing link between any other marker of inflammation and the radiographic phenotypes we defined.

Studies of the link between OA and CRP, the most-studied potential biomarker of OA, have had contradictory findings. In general, large population-based studies with adequate control for body mass have failed to find a convincing association[12,13,24], while those of selected OA populations, often using healthy controls, have found an association[4,7,8,14,25,26], although exceptions are found in both cases[5,11]. This suggests that at least some of the latter studies may suffer from residual confounding due to insurmountable differences between cases and controls. The findings from our study with regard to CRP would be consistent with this hypothesis.

However, 2 studies deserve special mention in this regard: Sowers and colleagues[27] in their population-based study suggested that, although the association of CRP with OA was greatly attenuated when adjusted for body mass, there could be remaining effect modification by CRP of the weight-OA association. (We were unable to find effect modification of any inflammatory marker by BMI.) Bos and colleagues[28] investigated the association of CRP haplotypes and both serum CRP levels and the development of OA. Although 1 haplotype (H7/8) was associated with both serum CRP and OA, serum levels of CRP were not associated with OA. Another recent report[24] found no association between CRP haplotype and OA. CRP haplotype in Bos and colleagues[28] appears to have served as an instrumental variable (Mendelian randomization), allowing the authors to detect a relationship with OA, while the serum level was too confounded to

Table 3. OR of radiographic osteoarthritis (ROA) using patient-centered definitions. OR data are for each definition of OA, using logistic regression and adjusted for age, sex, and BMI. Bold type indicates statistically significant associations ($p \leq 0.05$).

Marker	Thumb Base OA (KL > 1 in both joints)		MCP OA (KL > 1 in > 1 joint of each hand)		PIP OA (KL > 1 in > 3 joints of each hand)		DIP OA (KL > in > 3 joints of each hand)		Knee OA (KL > 1 both knees)	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Adiponectin	0.99	(0.83–1.18)	1.14	(0.60–2.19)	**1.54**	**(1.04–2.28)**	1.05	(0.76–1.44)	1.10	(0.85–1.43)
CD40 (serum)	1.02	(0.89–1.17)	1.38	(0.85–2.22)	1.26	(0.89–1.77)	1.13	(0.87–1.47)	1.22	(0.99–1.51)
CD40 (plasma)	0.96	(0.84–1.11)	0.66	(0.25–1.73)	1.18	(0.86–1.61)	0.88	(0.66–1.18)	0.95	(0.75–1.21)
CRP	0.97	(0.85–1.11)	0.86	(0.45–1.65)	1.00	(0.72–1.38)	**0.68**	**(0.47–1.00)**	1.08	(0.92–1.27)
Fibrinogen	1.00	(0.86–1.15)	1.14	(0.63–2.04)	1.11	(0.77–1.61)	0.77	(0.58–1.02)	0.87	(0.67–1.11)
ICAM-1	0.96	(0.84–1.10)	1.00	(0.62–1.61)	1.04	(0.75–1.43)	0.91	(0.70–1.18)	1.08	(0.90–1.31)
IL-6	1.02	(0.89–1.17)	**1.38**	**(1.00–1.89)**	0.76	(0.43–1.35)	**0.39**	**(0.20–0.75)**	0.92	(0.72–1.19)
Isoprostanes	0.98	(0.84–1.14)	0.42	(0.13–1.34)	0.97	(0.64–1.47)	1.08	(0.87–1.35)	1.14	(0.93–1.40)
LP-PLA_2 activity	0.91	(0.79–1.06)	0.47	(0.24–0.94)	1.18	(0.80–1.75)	1.11	(0.84–1.47)	1.08	(0.84–1.38)
LP-PLA_2 mass	1.04	(0.91–1.20)	0.89	(0.49–1.62)	1.20	(0.84–1.72)	0.96	(0.74–1.25)	0.89	(0.71–1.13)
MCP1	0.98	(0.86–1.12)	1.18	(0.89–1.55)	0.82	(0.52–1.29)	**1.19**	**(1.01–1.40)**	1.10	(0.93–1.31)
MPO	**1.21**	**(1.06–1.38)**	0.96	(0.52–1.79)	0.96	(0.62–1.48)	0.97	(0.72–1.31)	1.01	(0.81–1.27)
OPG	1.00	(0.87–1.15)	1.28	(0.87–1.90)	0.98	(0.70–1.38)	1.05	(0.83–1.31)	1.02	(0.82–1.27)
P-selectin	0.99	(0.86–1.13)	0.72	(0.37–1.39)	0.71	(0.47–1.09)	0.89	(0.69–1.15)	1.00	(0.81–1.23)
Resistin	0.92	(0.77–1.10)	0.57	(0.22–1.45)	1.13	(0.75–1.73)	1.15	(0.87–1.53)	0.90	(0.68–1.19)
TNF-α	1.01	(0.86–1.17)	0.71	(0.22–2.32)	0.80	(0.36–1.77)	0.93	(0.65–1.31)	1.04	(0.86–1.25)
TNF-RII	0.99	(0.86–1.14)	**1.49**	**(1.01–2.20)**	1.01	(0.73–1.40)	0.92	(0.72–1.17)	0.99	(0.80–1.23)

BMI: body mass index; KL: Kellgren and Lawrence grade; CD40: CD40 ligand; CRP: C-reactive protein; ICAM-1:intercellular adhesion molecule-1: IL-6: interleukin 6; isoprostanes: (urinary creatinine)/(8epi-PGF2a); LP-PLA_2: lipoprotein-associated phospholipase A_2; MCP1: monocyte chemoattractant protein; MPO: myeloperoxidase; OPG: osteoprotegerin; TNF-α: tumor necrosis factor-α; TNF-RII: type II TNF receptor; PIP: proximal interphalangeal; DIP: distal interphalangeal.

Table 4. Risk of radiographic osteoarthritis (ROA) using number of affected joints as the outcome. Linear regression analysis adjusted for age, sex, and body mass index. Joint score is total number of affected (KL > 1) joints.

Marker	Linear Regression Model (dependent variable = joint score)		Linear Regression Model (dependent variable = log of joint score)	
	B Coefficient*	p	B Coefficient**	p
Adiponectin	–0.028	0.86	0.005	0.88
CD40 (serum)	0.227	0.06	0.033	0.16
CD40 (plasma)	0.021	0.86	0.007	0.77
C-reactive protein	–0.053	0.67	–0.004	0.88
Fibrinogen	–0.143	0.26	–0.030	0.23
ICAM-1	0.047	0.69	–0.006	0.80
Interleukin 6	–0.054	0.65	0.007	0.77
Isoprostanes	0.008	0.96	–0.012	0.66
LP-PLA_2 activity	–0.042	0.75	–0.033	0.20
LP-PLA_2 mass	–0.086	0.47	–0.025	0.28
MCP1	0.085	0.48	0.012	0.61
Myeloperoxidase	0.149	0.21	0.037	0.11
Osteoprotegerin	0.114	0.38	0.009	0.73
P-selectin	–0.085	0.48	–0.002	0.92
Resistin	–0.026	0.86	–0.024	0.41
TNF-α	–0.037	0.79	–0.013	0.64
TNF-RII	0.163	0.20	0.013	0.59

* Change in no. SD needed to predict 1 additional joint affected. ** Change in no. SD needed to predict 1 additional log joint affected. KL: Kellgren and Lawrence grade; CD40: CD40 ligand; ICAM-1: intercellular adhesion molecule 1; IL-6: interleukin 6; isoprostanes: (urinary creatinine)/(8epi-PGF2a); LP-PLA_2: lipoprotein-associated phospholipase A_2; MCP1: monocyte chemoattractant protein; TNF-α: tumor necrosis factor-α; TNF-RII: type II TNF receptor.

Table 5. Effect of total number of affected joints on log (markers). Linear regression analysis adjusted for age, sex, and body mass index.

Marker	N in Analysis (Maximum n = 1235)	B Coefficient	p
Adiponectin	885	–0.001	0.78
CD40 (serum)	1211	0.022	0.03
CD40 (plasma)	1229	0.003	0.75
C-reactive protein	1226	–0.004	0.54
Fibrinogen	1227	–0.001	0.29
ICAM-1	1226	0.001	0.59
Interleukin 6	1225	–0.005	0.22
Isoprostanes	964	0.003	0.52
LP-PLA$_2$ activity	1227	–0.001	0.74
LP-PLA$_2$ mass	1227	–0.001	0.67
MCP1	1208	0.000	0.97
Myeloperoxidase	1182	0.007	0.10
Osteoprotegerin	1227	0.001	0.66
P-selectin	1229	0.003	0.27
Resistin	876	0.000	0.97
TNF-α	877	0.000	0.90
TNF-RII	1194	0.003	0.12

CD40: CD40 ligand; ICAM-1: intercellular adhesion molecule 1; isoprostanes: (urinary creatinine)/(8epi-PGF2a); LP-PLA$_2$: lipoprotein-associated phospholipase A$_2$; MCP1: monocyte chemoattractant protein; TNF-α: tumor necrosis factor-α; TNF-RII: type II TNF receptor.

observe this effect. We would argue that these 2 studies suggest that while CRP genotype could be associated with the development of OA, this relationship is highly confounded by the relationship between CRP and body mass. This would make CRP a poor biomarker for the development of OA in clinical situations.

That we were unable to find a consistent relationship between inflammatory markers and OA after adjustment for BMI, which has a relatively weak association with systemic inflammation, suggests that the inclusion of a measure of body habitus with a stronger relationship to inflammation, such as waist circumference, would not have changed our results.

Regarding the relationship between other inflammatory markers and OA, there are a number of reasons why our findings might not agree with other reported associations. First, it is possible that certain OA phenotypes are more likely to be associated with higher levels of inflammation and that these phenotypes are more likely to be identified using blood-derived markers. Studies of rapidly progressive hip OA[7] or "erosive" hand OA[8,18], for example, may reflect discrete OA subtypes in which local inflammation plays an especially important role and is significant enough to be reflected in the serum.

Second, some studies have suggested that clinically detected OA-associated synovitis[15], or synovitis detected in pathologic specimens[9], are more likely to be associated with painful OA phenotypes, and that these phenotypes may in turn be more highly associated with markers of systemic inflammation. Another study[10] found that CRP was more associated with degree of pain in OA rather than radiographic disease, further supporting this hypothesis. Our sensitivity analysis did not find any association between CRP and symptomatic OA (although comparatively strong associations between some definitions of symptomatic OA and fibrinogen, IL-6, and LP-PLA$_2$ might warrant further investigation).

Third, publication bias could be a source of previously reported associations. For instance, we identified some associations that we believe are due to chance. Some of these associations were weak (e.g., MCP-1, myeloperoxidase), while others gave opposite effects depending on OA phenotype (a negative association between IL-6 and PIP joint OA, but a positive association with MCP joint OA), making their interpretation problematic. Stronger associations (e.g., TNF-RII and adiponectin) could reflect chance associations given that we investigated 17 different markers in multiple models. It is possible that other authors published their more interesting results, while less interesting or negative associations were not published. It is intriguing, however, that some of the associations we found have been reported by other authors including those for TNF-RII[14], IL-6[14,15], and adiponectin[18] (the latter, interestingly, in a similar phenotype of hand OA). Further research into these markers in appropriate datasets might be of value to help clarify whether these relationships are due to chance or are true.

Fourth, timing may play an important role. In most studies, the inflammatory marker was tested in patients with active OA. This may not have been the case in our study, in which blood was drawn some years before radiographs were taken; some patients may not have had OA yet or may have been developing OA at the time of the blood draw. On the other hand, at least 1 study has suggested that a rise in CRP may precede radiographic disease by some years[29]; thus it could be preferable to have blood drawn prior to disease onset. Therefore, it is difficult to be sure how to interpret this apparent limitation.

Finally, it is possible that differences with other published results reflect the limitations of our cross-sectional study design. We did not, for example, evaluate changes in inflammatory marker levels or in the degree of ROA over time. For example, 1 study found that elevated CRP levels were associated with more rapid progression of disease[5]. Our study did not examine changes in markers or joints over time.

We have shown that in general, serum inflammatory markers are poorly associated cross-sectionally with radiographic arthritis of the hands and/or knees. A few markers, including IL-6, adiponectin, LP-PLA$_2$, and TNF-RII, may warrant further investigation as markers for some OA phenotypes. Additionally, further study is needed to establish whether any of these markers would perform better as markers of more aggressive disease.

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