Inflammatory Markers and Physical Function Among Older Adults with Knee Osteoarthritis

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ABSTRACT. ***Objective.*** To investigate whether serum concentrations of various inflammatory markers are associated with physical function and disease severity among older obese adults with knee osteoarthritis (OA).

Methods. Data are from baseline assessments in 274 patients with knee OA participating in an exercise and nutrition intervention study. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) was used to assess self-reported physical function, pain, and stiffness. The presence of disability was assessed, walking speed was calculated on the basis of the 6-minute walk test, and knee radiographs determined the radiographic severity of OA. Serum concentration of interleukin 6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and the soluble receptors IL-6sR, IL-2sR, TNF-sR1 and TNF-sR2 were measured by ELISA.

Results. In multivariate regression analyses adjusted for age, sex, race, body mass index, comorbid conditions, and use of nonsteroid antiinflammatory drugs, higher serum levels of TNF-sR1 and TNF-sR2 were significantly associated with lower scores on the WOMAC physical function, with more symptoms of pain and stiffness, and with more reported physical disability. In addition, higher serum levels of TNF-sR1 and TNF-sR2 were significantly associated with slower walking speed, and tended to be associated with worse radiographic scores. Higher serum levels of IL-6 tended to be associated with slower walking speed, but no significant associations were observed for CRP, IL-6sR, or IL-2sR.

Conclusion. Especially high levels of the soluble receptors of TNF-α were found to be associated with lower physical function, increased OA symptoms, and worse knee radiographic scores in older obese adults with knee OA. (J Rheumatol 2004;31:2027–31)

Key Indexing Terms:
INFLAMMATION
OSTEOARTHRITIS
SOLUBLE TUMOR NECROSIS FACTOR-α RECEPTORS
PHYSICAL FUNCTION

Inflammation is a necessary response of the immune system to different stimuli such as infection and injury, resulting in elevated production of cytokines and acute-phase proteins. However, chronic activation of these pathways is associated with serious detrimental effects. Increased serum concentrations of inflammatory markers, such as interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP), have been implicated in the pathophysiology of coronary heart disease[1,2] and have been shown to predict the onset of physical limitations over time[3-6]. Unlike rheumatoid arthritis, osteoarthritis (OA) has traditionally been considered a noninflammatory disease. However, recently, various studies indicate the presence of intraarticular inflammation by synovitis, and that this low grade inflammation plays a pathophysiological role in the disease process of OA[7-9]. An inflammatory component associated with OA can be detected in the serum, since serum concentrations of inflammatory markers such as CRP and IL-6 are higher among persons with knee or hip OA, compared to a population without OA[10,11]. In particular, TNF-α appears to play a predominant role in the initiation and progression of articular cartilage destruction[12].

The soluble receptors of proinflammatory cytokines may also play an important role in the deleterious effects of the inflammation process. There is some evidence that stimuli causing cytokine concentrations to rise may also induce shedding of cytokine soluble receptors, some of which enhance the activity of the cytokines[13-15]. In addition, since soluble cytokine receptors are generally more stable in circulation over time than cytokines[16,17], they could potentially be more reliable markers of chronic inflammation.

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A longitudinal study by Sharif, *et al*[18] found that high serum levels of CRP at one timepoint predicted increased radiographic progression of knee OA 3 and 5 years later. However, whether increased serum levels of inflammatory markers are associated with OA disease severity and physical function measured by mobility, pain, stiffness, and radiographic progression has not been extensively examined. We investigated whether several inflammatory markers (IL-6, CRP, TNF-α, and the soluble receptors IL-6sR, IL-2sR, TNFsR1, and TNFsR2) are associated with poorer physical function performance and more disability, pain, stiffness, and radiographic progression in older men and women with knee OA.

MATERIALS AND METHODS

Study design and sample. We analyzed baseline data from 274 older, overweight adults with knee OA who were recruited for participation in a single-blind, randomized controlled clinical trial (Arthritis, Diet and Activity Promotion Trial, ADAPT) designed to compare the effects of 18 months of exercise and dietary weight loss (diet) alone or in combination on physical function. The study was conducted at the Wake Forest University School of Medicine Claude D. Pepper Older Americans Independence Center with the approval of the university's institutional review board. The design and the sample of the study have been described in detail[19,20].

Briefly, the eligibility criteria for participation in the study were: (1) age ≥ 60 years, (2) body mass index (BMI) ≥ 28 kg/m^2, (3) knee pain on most days of the month, (4) sedentary lifestyle (< 20 min of formal exercise per week for the past 6 months), (5) self-reported difficulties with mobility or self-care activities, and (6) radiographic evidence of tibiofemoral OA based on weight-bearing anteroposterior radiographs. Participants were excluded when they had a serious medical condition that prevented safe participation in an exercise program. A total of 2209 older adults were prescreened via telephone interviews. Of these, 1596 did not meet eligibility criteria and 297 refused further contact. Eventually, 316 participants were randomized for study. Persons with missing data on inflammatory markers were excluded, leaving 274 subjects for the present analyses.

Inflammatory markers. Blood was collected in the morning (between 7 and 9 A.M.) via venipuncture after an overnight fast. Serum concentrations of IL-6, CRP, TNF-α, and the soluble receptors IL-6sR, IL-2sR, TNF-sR1, and TNF-sR2 were determined by ELISA. All samples were measured in duplicate and the average of the 2 values was used for data analysis. Duplicate samples that did not provide a coefficient of variation < 15% were reanalyzed and all values were averaged for data analysis. Cytokines and soluble receptors were measured using Quantikine high-sensitivity immunoassay kits (R&D Systems, Minneapolis, MN, USA). In our laboratory, the interassay and intraassay coefficients of variation (CV) for IL-6 were 7.3% and 3.5%, respectively, for TNF-α were 11.8% and 6.2%, and were under 5% for the soluble receptor assays. The interassay and intraassay CV for the CRP assay (Alpco, Windham, NH, USA) were 8% and 6.7%, respectively.

Disease severity and physical function indicators

Western Ontario and McMaster University Osteoarthritis index (WOMAC). The WOMAC[21] was used to assess self-reported physical function, pain, and stiffness. The WOMAC uses 17 questions concerning the degree of difficulty performing activities of daily living to assess physical function. Each question asks the participant to indicate on a scale from 0 (none) to 4 (extreme) the degree of difficulty he/she has experienced in the last 48 hours due to knee OA. Individual scores were averaged to generate a summary score ranging from 0 to 4. For pain, 5 questions asked how much pain they experienced due to the arthritis during the following activities: walking, stair ascent and descent, at night in bed, sitting or lying, and standing. For stiffness, 2 questions were asked regarding the severity of stiffness after first awakening in the morning and after sitting or resting later in the day. The individual scores were averaged to generate a summary score for both pain and stiffness.

Physical disability. Physical disability was measured by the self-reported FAST functional performance inventory[22]. This measure uses 23 questions to assess perceived difficulty with a number of activities including basic activities of daily living (ADL), instrumental ADL, ambulation, transferring, and upper extremity strength. For each activity, participants were asked: "How much difficulty, if any, do you have doing [name of activity] over the past month because of your health?" The scale for each question ranged from 1 (no difficulty) to 5 (unable to do). Averaging the score of all items created a composite score. The composite index has an alpha reliability of 0.79.

Walking speed. The distance walked in 6 minutes was used as a physical performance task to assess walking speed. Participants were asked to perform this task as quickly as possible without wearing a watch. No cues or encouragement were given during the testing.

Radiographic evidence of knee OA. Anterior-posterior standing knee radiographs were obtained to determine the effects of intervention on radiographic disease. Knee radiographs were read by a single physician. Severity of knee OA was assessed using a classification scheme adapted from Altman, *et al*[23]. Both the medial and lateral compartments were graded for osteophytes, subchondral cysts, and joint space narrowing on a 0–3 Likert scale using an atlas. The scores for each feature were added to compute a summary score from 0 (low radiographic severity) to 24 (high severity) for the most affected knee.

Covariates. Sociodemographic information used in the analyses included age, sex, and race. Body mass index was calculated by assessed weight (kg) divided by square of height (m^2). Comorbid conditions were assessed by self-reported presence of heart disease, lung disease, diabetes, and cancer. In addition, the use of nonsteroidal antiinflammatory drugs (NSAID) was assessed by the medication observation method. All respondents were asked to bring their medications to study assessment visits, and they were then recorded.

Statistical analyses. Correlations between inflammatory markers were described using Spearman correlation coefficients. Since concentrations of all inflammatory markers (except IL-2sR and IL-6sR) were not normally distributed, log-transformed values were used in the analyses. Linear regression was used to examine the link between (log-transformed) inflammatory marker levels and physical function and disease outcomes. These analyses were adjusted for age, sex, race, BMI, NSAID use, and comorbid conditions.

RESULTS

Main characteristics of the sample population are shown in Table 1. Participants were on average 68.4 years old and had a mean BMI of 34.2 kg/m^2. The majority of the sample (71.9%) was female. The median level of CRP was 0.42 µg/ml, for IL-6, 3.61 pg/ml, and for TNF-α, 2.03 pg/ml. As shown in Table 2, IL-6 levels were significantly correlated with CRP levels (Spearman r = 0.32) and TNF-α levels (Spearman r = 0.23). There was no significant correlation between CRP and TNF-α levels. The highest correlation was found between the soluble receptors TNF-sR1 and TNF-sR2 (Spearman r = 0.81). Both these soluble receptors were also significantly associated with IL-6, TNF-α, and IL-6sR (Table 2).

Table 3 shows the results of linear regression analyses examining the link between inflammatory marker concentrations (log-transformed except for IL-1sR and IL-6sR) and

Table 1. Baseline characteristics (n = 274).

Age, mean yrs ± SD	68.4 ± 6.20
Female, %	71.9
Race, %	
White	77.7
Black	20.4
Other	1.8
BMI, mean kg/m^2 ± SD	34.2 ± 5.1
Comorbidity, %	
Coronary heart disease	42.3
Congestive heart failure	3.6
Diabetes	9.1
Cancer	14.2
Lung disease	16.8
Use of NSAID	44.2
WOMAC physical function, mean score ± SD	1.42 ± 0.68
WOMAC pain, mean score ± SD	1.37 ± 0.69
WOMAC stiffness, mean score ± SD	1.85 ± 0.73
Physical disability, mean score ± SD	1.99 ± 0.58
Walking speed, mean m/s ± SD	1.18 ± 0.22
Radiography score, mean score ± SD	2.24 ± 0.82
Inflammatory markers	
CRP, median µg/ml (IQR)	0.42 (0.20–0.87)
IL-6, median pg/ml (IQR)	3.61 (2.49–5.60)
TNF-α, median pg/ml (IQR)	2.03 (1.46–3.00)
IL-6sR, median mg/ml (IQR)	34.94 (27.81–42.60)
IL-1sR, median mg/ml (IQR)	12.31 (10.51–15.77)
TNF-sR1, median pg/ml (IQR)	1417 (1121–1704)
TNF-sR2, median pg/ml (IQR)	2649 (2177–3175)

IQR: inter quartile range. BMI: body mass index; NSAID: nonsteroidal antiinflammatory drugs; WOMAC: Western Ontario and McMaster University Osteoarthritis Index; CRP: C-reactive protein; IL-6sR: interleukin 6 soluble receptor; TNF-α: tumor necrosis factor-α.

the WOMAC scores, adjusted for age, sex, race, BMI, NSAID use, and comorbid conditions. Higher levels of the soluble receptors TNF-sR1 and TNF-sR2 were significantly associated with higher scores on the WOMAC physical function, indicating poorer function (ß = 0.334, p = 0.01 and ß = 0.391, p = 0.004, respectively). Higher serum levels of TNF-sR1 and TNF-sR2 were also significantly associated with more pain (ß = 0.360, p = 0.01 and ß = 0.446, p = 0.002 respectively). In addition, TNF-sR2 was found to be significantly and positively associated with more stiffness (ß = 0.309, p = 0.04). The only other association with WOMAC scores was found for TNF-α and WOMAC function (ß = –0.103, p = 0.03).

Table 4 shows the results of similar analyses for physical disability, walking speed, and radiographic score. Consistent with previous findings for the WOMAC function score, higher levels of TNF-sR1 and TNF-sR2 were significantly associated with higher physical disability scores (ß = 0.371, p < 0.001 and ß = 0.400, p < 0.001, respectively). A borderline significance was found for TNF soluble receptors and poor radiography scores (p = 0.08 for both TNF-sR1 and TNF-sR2). Higher IL-6 levels were moderately associated with poorer walking speed (ß = –0.036, p = 0.08). Although higher levels of TNF-sR1 and TNF-sR2 showed a negative regression coefficient for the walking speed outcome, these associations did not reach statistical significance (p = 0.22 and p = 0.20, respectively).

DISCUSSION

We examined the relationship between several inflammatory markers and soluble receptors and physical function, pain, stiffness, and physical performance in an older, obese population with knee OA. This study provides evidence that, in patients with knee OA, especially higher levels of the TNF soluble receptors are indicative of poor physical function. High levels of these receptors were also associated with more pain and increased stiffness, and tended to be associated with higher radiographic severity of knee OA. Higher serum concentrations of IL-6 tended to be associated with slower walking speed.

Studies have shown associations of the inflammatory markers IL-6 and CRP with functional decline and disability in general samples of older persons[3-5]. However, to our knowledge, no study has specifically examined the association of a variety of inflammatory markers with physical function and disease symptom measures in older persons with OA. In our patients with knee OA, we could not confirm a very strong and consistent association between serum levels of IL-6 and CRP and physical function measures. Higher IL-6 levels were associated with slower walking speed, but not with other outcomes. Westacott and Sharif identified a dual role for IL-6 in the pathophysiology of joint diseases, with both destructive and protective mechanisms[24]. Such a dual role could explain why we did not find a very consistent association for IL-6 with all physical function and disease severity outcomes, as described in other older

Table 2. Spearman correlations between levels of inflammatory markers.

	CRP	IL-6	TNF-α	IL-6sR	IL-1sR	TNF-sR1
CRP	—					
IL-6	0.314**	—				
TNF-α	–0.034	0.228**	—			
IL-6sR	–0.072	0.153*	0.196**	—		
IL-1sR	–0.001	0.011	0.001	0.071	—	
TNF-sR1	0.098	0.295**	0.187**	0.193**	0.026	—
TNF-sR2	0.052	0.296**	0.278**	0.199**	0.069	0.806**

* p < 0.05; ** p < 0.01. For definitions, see Table 1.

Table 3. Adjusted* regression coefficients (Reg Coeff) for the association between inflammatory marker levels and WOMAC scale scores.

Inflammatory Markers**	WOMAC Function Reg Coeff	p	WOMAC Stiffness Reg Coeff	p	WOMAC Pain Reg Coeff	p
CRP	–0.015	0.59	–0.043	0.17	0.018	0.54
IL-6	–0.020	0.77	–0.015	0.85	0.097	0.18
TNF-α	–0.103	0.03	–0.080	0.13	–0.068	0.18
IL-6sR	–0.001	0.86	0.004	0.39	0.006	0.12
IL-1sR	–0.007	0.42	0.001	0.92	–0.002	0.84
TNF-sR1	0.334	0.01	0.190	0.21	0.360	0.01
TNF-sR2	0.391	0.004	0.309	0.04	0.446	0.002

* Adjusted for age, sex, race, BMI, coronary heart disease, congestive heart failure, diabetes, cancer, lung disease, NSAID use. ** Per log-unit increase (except for IL-1sR and IL-6sR). For definitions, see Table 1.

Table 4. Adjusted* regression coefficients (Reg Coeff) for the association between inflammatory marker concentrations and disability, walking speed, and radiographic score.

Inflammatory Markers**	Disability Score Reg Coeff	p	Walking Speed Reg Coeff	p	Radiography Score Reg Coeff	p
CRP	–0.028	0.26	–0.008	0.37	–0.0004	0.99
IL-6	–0.0002	0.99	–0.036	0.08	–0.051	0.63
TNF-α	–0.043	0.30	0.021	0.13	0.035	0.67
IL-6sR	0.001	0.84	0.0003	0.78	0.003	0.67
IL-1sR	0.002	0.81	–0.001	0.74	–0.009	0.53
TNF-sR1	0.371	0.002	–0.052	0.22	0.329	0.12
TNF-sR2	0.400	0.001	–0.055	0.20	0.347	0.11

* Adjusted for age, sex, race, BMI, coronary heart disease, congestive heart failure, diabetes, cancer, lung disease, NSAID use. ** Per log-unit increase (except for IL-1sR and IL-6sR). For definitions, see Table 1.

populations[3]. In agreement with a study by Uson, *et al*[25], we also found no correlation between serum levels of the IL-6 soluble receptor and disease symptoms and functional status. For serum CRP levels, we did not find any significant association with the physical and disease status. This finding is in accord with findings in a study of 67 patients with knee OA[26], but contrasts with a study by Wolfe, who found that serum CRP levels in patients with knee and hip OA were associated with clinical severity and functionality[27]. However, Wolfe studied clinic patients with more severe disease, who showed overall a higher median value of CRP (5.9 compared to 4.2 mg/ml in our study), which may explain the inconsistency in study findings. In a study by Otterness, *et al*[28], serum CRP levels were correlated with joint swelling, but not with other baseline clinical assessments.

There is evidence that TNF-α and its soluble receptors have a direct mediating effect on the disease progression of OA[29,30]. In a study by Alaaeddine, higher expression of soluble receptors of TNF-α in human OA synovial fibroblasts was found to mediate the biological activation by TNF-α[30]. Moreover, soluble receptors of TNF-α increase TNF-α induced prostaglandin E_2 and cyclooxygenase 2 (COX-2) production[30]. In addition, at sites where chondrocyte expression of soluble TNF-α receptors is high, higher levels of TNF-α could cause focal loss of cartilage[30,31].

Our findings show that associations with physical function and disease symptoms were stronger for levels of soluble receptors of TNF-α than for the level of TNF-α itself[17]. TNF-α is a proinflammatory cytokine that is very sensitive to subtle changes in endogenous glucocorticoid levels, such as circadian variations, and has a rather short half-life. There is some evidence that stimuli causing cytokine levels to rise may also induce shedding of cytokine soluble receptors, some of which enhance the activity of the cytokines[13-15]. Soluble cytokine receptors are generally more stable in the circulation over time than cytokines[16], and are thought to reflect previous biological effects of TNF-α, and therefore could be more representative of the inflammatory response. In addition, some studies report that TNF-α shows a detrimental disease activity only when there is a high expression of TNF-α receptors[32]. This may also explain why the soluble receptors are more strongly associated with physical function and disease severity indicators. A possible role for TNF-sR2 in knee OA is supported by the finding by Otterness, *et al*[33] that the serum level of TNF-sR2 is significantly higher in OA patients compared to controls.

We did not assess serum levels of IL-1ß, which may be implicated in the pathophysiology of joint diseases as well[24]. The serum level of IL-1 soluble receptor was assessed in our study, but was not found to be related to disease severity and physical function outcomes. Another shortcoming of our study is its cross-sectional design, which makes it impos-

sible to elucidate causality in the associations we found. Therefore, it is not possible to conclude whether inflammatory markers are mediators or markers of joint destruction.

However, despite the limitations, our study shows that higher serum concentrations of the TNF-α soluble receptors are associated with physical function and disease symptoms in patients with knee OA. This suggests the importance of TNF-α and its soluble receptors in the disease progress of knee OA, and indicates that there is an inflammatory component associated with OA that can be detected in the serum. Future studies are needed to examine whether therapeutic intervention on the inflammatory component can prevent functional decline and disease progress in patients with OA.

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