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Original Article

Relationship between serum and synovial fluid CCL20 concentrations with disease severity in primary knee osteoarthritis

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Abstract

Objectives: The current study was performed to examine serum and synovial fluid (SF) CCL20 levels and their correlations with disease severity in primary knee osteoarthritis patients. **Methods:** A total of 99 patients diagnosed with primary knee OA were enrolled in the study, and 95 healthy individuals receiving regular medical examination were recruited as controls. Serum and SF CCL20 concentrations were determined using an enzyme-linked immunosorbent assay. The radiographic severity of OA was assessed by the Kellgren-Lawrence (K-L) classification system. The Lequesne algofunctional index and a visual analogue scale (VAS) were used to evaluate the clinical severity of knee OA in patients. **Results:** The serum CCL20 levels were not significantly different between patients with knee OA and controls. Patients with a K-L grade of 4 had significantly higher SF CCL20 levels than those with K-L grades of 2 and 3. Knee OA patients with a K-L grade of 3 showed significantly higher levels of CCL20 in SF than those with a K-L grade of 2. In addition, SF CCL20 levels were significantly related to the Lequesne algofunctional index and VAS score. **Conclusions:** These findings suggest that local CCL20 levels may reflect the disease severity of knee OA.

Keywords: Chemokine C-C Motif Ligand 20, Macrophage Inflammatory Protein 3α, Knee Osteoarthritis, Disease Severity, Biomarker

Introduction

Osteoarthritis (OA) is the most highly prevalent joint disease and is characterized by progressive articular cartilage degradation, secondary synovitis and subchondral sclerosis[1]. Primary knee OA is the most common type of OA and often causes a heavy burden of pain and functional disability, including high costs of treatments, decreased productivity, and absence from work[2]. The etiology of knee OA remains poorly understood[3], and risk factors, including obesity, previous injury, sex, advancing age, and quadriceps weakness, may differ in their mechanisms of action[4]. According to one study from 2010, it is estimated that 37% of US individuals over 60 years of age suffer from radiographic evidence of knee OA and that 12% have symptoms related to knee OA accompanying radiographic findings[5]. In China, one longitudinal study showed that the incidence of total symptomatic knee OA was 8.1%[6], indicating that knee OA is a common disease with high morbidity in China.

Evidence has been established that the original driver for the development of OA involves not only simple mechanical "wear and tear", but also crucial roles played by inflammatory components in OA progression[7]. Current treatments for OA only control the symptoms, and none have been FDA-approved for the prevention or slowing of disease progression[8]. However, increasing insight into the inflammatory underpinnings of OA holds promise for the

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development of new, disease-modifying therapies[9].

Chemokines, one group of the most important inflammatory cytokines, are composed of 8-12 kD peptides and are generally classified into four families (C, CC, CXC, and CX3C) according to the number and spacing of cysteine residues within their N-terminal regions[10]. The vast majority of chemokines belong to the CC and CXC families, and they exert their cellular effects by binding to G protein-coupled cell surface receptors[11]. Among the CC family, MIP-3α (CCL20) is a CC chemokine expressed in a variety of cells, including dendritic cells, monocytes, granulocytes, T and B cells, and endothelial cells[12,13]. A series of studies have demonstrated that CCL20 is also related to many chronic inflammatory diseases, including atopic dermatitis, and inflammatory disease in the central nervous system, thus implicating their potential role in inflammatory responses[14,15]. Previous findings have mainly focused on the role of CCL20 in the development of synovitis in rheumatoid arthritis[16]. CCL20 has been identified to be highly expressed in chondrocytes[17], and CCL20 could affect the chondrocyte actin cytoskeleton via the Rho-Rho kinase pathway[17]. CCL20 protein expression was higher in OA cartilage sections than in donor sections, as determined by immunohistochemistry[18]. Moreover, CCL20 mRNA expression was low in donor chondrocytes but increased after stimulation with proinflammatory cytokines[18]. In addition, CCL20 and its receptor CCR6 have been studied in osteoblast proliferation and osteoclast differentiation in the homeostasis of subchondral bone during the process of arthritis[19].

Collectively, the above findings suggest that CCL20/MIP-3α may play important roles in OA progression. However, to the best of our knowledge, there have been no previous studies investigating the relationship between serum and synovial fluid(SF) levels of CCL20/MIP-3α and disease progression in knee OA patients. Therefore, the aim of the present study was to explore whether serum and SF levels of CCL20/MIP-3α are correlated with disease severity in knee OA patients.

Patients and methods

Study patients

From August 2017 to August 2018, 99 patients with primary knee OA receiving hyaluronate injections or total knee replacement were enrolled in the study. Knee OA was diagnosed based on the clinical and radiological criteria of the American College of Rheumatology[20]. For each patient, the diagnosis was confirmed by an evaluation of the patient's medical history, a physical examination, radiographic studies, or a combination of these methods. Patients were excluded from the study if they had secondary OA due to trauma or deformity; metabolic disorders such as diabetes mellitus, thyroid disorders, or renal failure with or without dialysis; infectious disorders such as septic arthritis, viral arthritis, or fungal arthritis; other potential conditions associated with inflammatory arthritis such as gout, pseudogout, hydroxyapatite or calcium pyrophosphate deposition disease, rheumatoid arthritis, systemic lupus erythematosus, or malignancy; or bilateral knee replacement. In addition, 95 sex- and age-matched individuals receiving regular medical examinations from both Handan Central Hospital and the third Hospital of Shi Jiazhuang were enrolled as healthy controls. All healthy controls had no history of knee OA disease, no signs of radiographic primary knee OA confirmed by X-ray and no complaints of knee pain or OA-related symptoms. Informed consent in accordance with the guidelines of the ethical committee of Handan Central Hospital was obtained from all study participants.

Radiographic assessment

Radiographic severity was evaluated by anteroposterior knee X-ray examination with the patient in a standing position and was graded according to the Kellgren-Lawrence (KL) scale (grades 0-4): grade 0, no radiographic features of OA are present; grade 1, possible narrowing of the joint space and osteophytic lipping; grade 2, definite osteophyte formation and possible narrowing of the joint space; grade 3, moderate osteophyte formation, definite narrowing of the joint space, some sclerosis and possible bone contour deformity; and grade 4, large osteophytes, marked narrowing of the joint space, severe sclerosis and definite bone contour deformity[21]. Only knee OA patients with K-L grades of ≥2 were considered to be significant and enrolled. If a patient had bilateral knee OA, the more affected knee was defined as the study knee. The X-ray was read by two orthopedic experts in our hospital in a blinded manner. The *kappa* value was used to examine the consistency of the assessment.

Evaluation of symptomatic severity

Symptomatic severity was evaluated by the VAS score and Lequesne algofunctional index. For the VAS score, all patients were asked to rate their pain intensity on a 10 cm visual analog scale with the 0 cm point suggesting "no pain" and the 10 cm point indicating the "worst possible pain"[22]. The Lequesne Algofunctional Index was used to evaluate symptomatic severity through the assessment of pain/discomfort, maximum distance walked, and activities of daily living, with a maximum index score of 24[23]. Both scales are reliable and are widely used based on clinical evidence and experience.

Enzyme-linked immunosorbent assay (ELISA) for serum and SF CCL20/MIP-3α levels

Synovial fluid was aspirated from the affected knee using sterile knee puncture just prior to hyaluronate injection or surgery, centrifuged to remove cells and joint debris, and stored immediately at -80°C before measurement. Blood samples were collected in the morning at 7:00. Blood samples were also collected from healthy subjects. Serum samples were then obtained by centrifugation at 3,000

Table 1. Demographic statistics.

	OA patients (n=99)	Healthy controls (n=95)	*P* value
Age (Y)	62.1±5.8	61.1±3.2	0.265
Sex (F/M)	41/58	44/51	0.492
BMI (kg/m^2)	24.5±2.8	24.2±2.2	0.116
Lequesne Index	10.3±4.0	/	
VAS score	5.2±1.9	/	
K-L grading (2/3/4)	34/34/31	/	
Serum CCL20 levels (pg/mL)	131.7±28.7	127.1±25.1	0.311
SF CCL20 levels (pg/mL)	346.4±61.2	/	
All data are expressed as the mean value±SD.			

× g for 10 min and stored at -80°C until analysis. The SF and serum CCL20 concentrations were measured by a commercially available ELISA, based on the manufacturer's instructions (R&D Systems, Minneapolis, MN). In the current study, the intraassay variation of this method was 4.2% and the interassay variation was 7.3%, with a spike recovery of 99%. All samples were routinely tested three times, and the results were averaged.

Statistical analysis

Statistical analysis was performed using GraphPad Prism version 6.0. Data are expressed as the means±standard deviations (SDs) or medians (interquartile ranges). Data normality was examined by the Kolmogorov-Smirnov test. Basic statistics between knee OA patients and healthy controls were compared by Chi-square tests, unpaired Student's t-tests, or Mann-Whitney U tests as appropriate. Comparison of the characteristics among different patients in the K-L subgroups was performed by one-way ANOVA or the Kruskal-Wallis test, depending on the data distribution. Bartlett's test was applied to examine the group variance homogeneity with the Tukey or Tamhane test for post hoc analysis. Associations between the serum and SF levels and the VAS score as well as the Lequesne Algofunctional Index were determined by the Spearman or Pearson correlation method. To adjust for potential confounders, regression analysis for adjusted models was then performed and included sex, BMI and age. *P*-values<0.05 were considered statistically significant.

Results

Demographic data

Demographic data of the enrolled participants are described in Table 1. The primary knee OA group included 41 men and 58 women aged 50-75 years (mean±SD, 62.1±5.8 years), with a mean ± SD body mass index (BMI) of 24.5±2.8 kg/m^2. The distribution of each K-L grade over all 99 knees was as follows: 34, grade 2; 34, grade 3; and 31, grade 4. The healthy control group comprised 44 males and 51 females

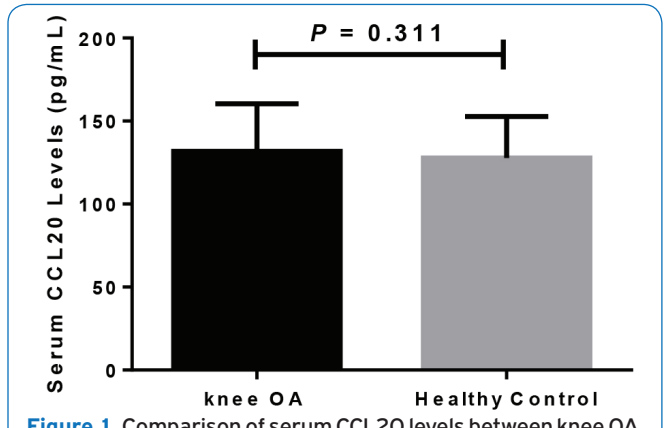

Figure 1. Comparison of serum CCL20 levels between knee OA and healthy control group.

aged 52-73 years (mean ± SD, 61.1±3.2 years), with a mean ± SD body mass index (BMI) of 24.2±2.2 kg/m^2. There was no significant difference in age, sex distribution, or BMI between the primary knee OA patients and healthy controls. The serum CCL20 levels between patients with OA and healthy controls were not significantly different (131.7±28.7 pg/mL vs. 127.1±25.1 pg/mL, *P*=0.311) (Table 1; Figure 1). There was also no significant difference between males and females (336.7±56.7 pg/mL vs. 353.3±63.8 pg/mL, *P*=0.185). In addition, no difference in the CCL20 level was found between patients aged ≥61 (median age, years) and those aged <61 (age ≥61 vs. age <61: 348.5±61.2 pg/mL vs. 343.3±41.4 pg/mL, *P*=0.633:). Last, no significant difference was found between patients with BMI≥24.4 (median BMI) and those with BMI<24.4 (BMI≥24.4 vs BMI<24.4: 353.1±45.1 pg/mL vs 336.7±56.7 pg/mL, *P*=0.128).

Association of CCL20 levels with radiographic severity

The *kappa value* was 0.85 for the consistency of the radiographic assessment. One-way ANOVA showed

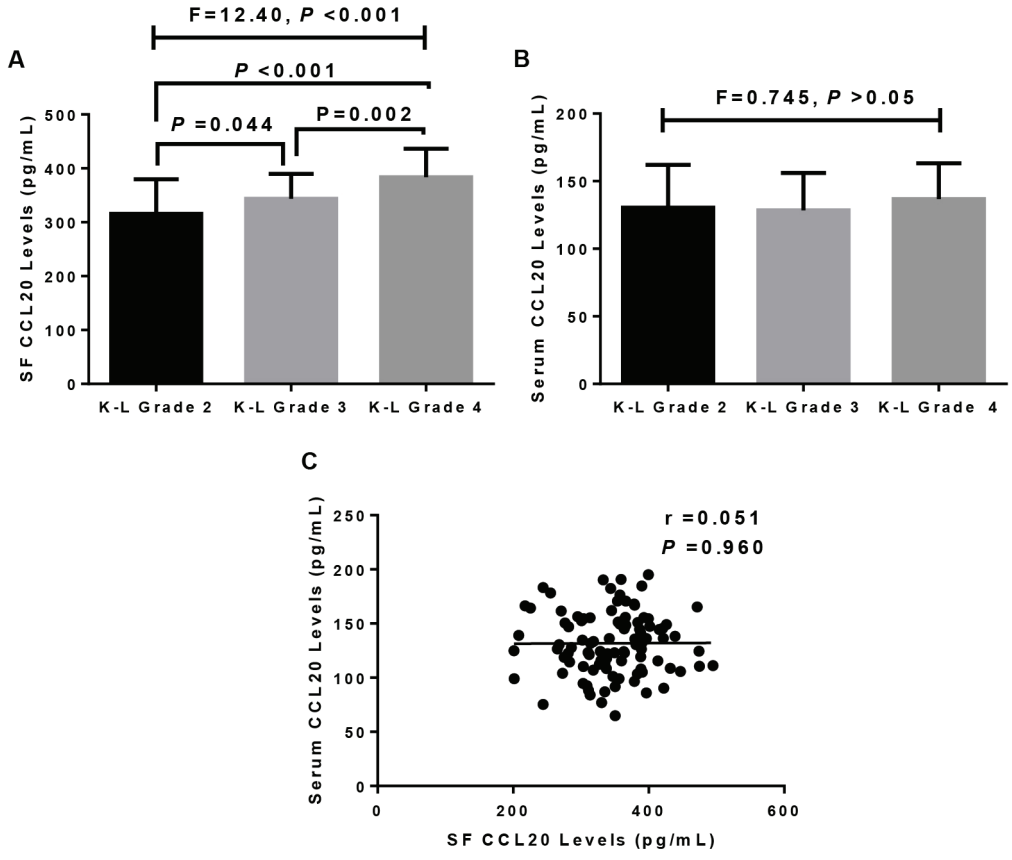

Figure 2. **A.** Comparison of SF CCL20 among different K-L grades. **B.** Comparison of serum CCL20 among different K-L grades. **C.** Correlation of serum CCL20 levels with SF CCL20 levels.

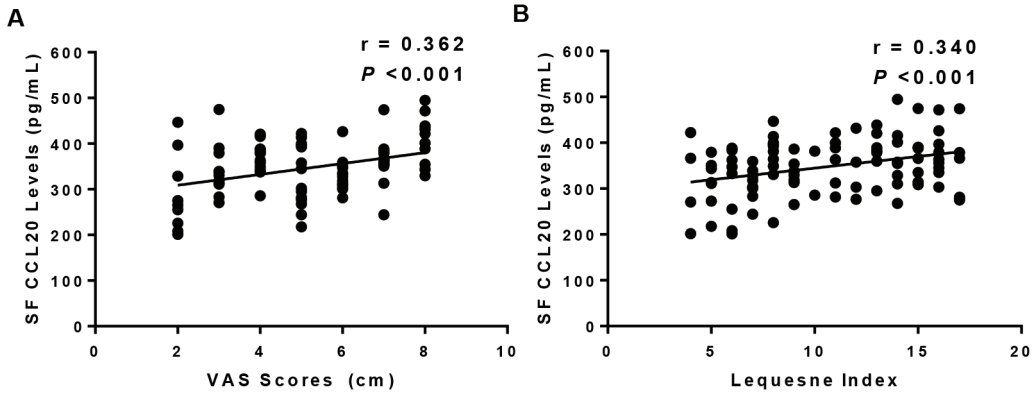

Figure 3. Relationship between SF CCL20 levels and clinical severity. **A.** Correlation of SF CCL20 levels with VAS score. **B.** Correlation of SF CCL20 levels with Lequesne index.

that there were significant differences among the three subgroups (F=12.40, *P*<0.001). *Post hoc* analysis indicated that the SF CCL20 levels were significantly higher in primary knee OA patients with a K-L grade of 3 than in those with a grade of 2 (343.4±46.4 pg/ml vs 316.0±64.6 pg/ml, *P*=0.044). In addition, the SF CCL20 levels were significantly elevated in K-L grade 4 patients compared with those in patients with K-L grades of 3 or 2 (383.5±53.1

Table 2. Linear regression model adjusted by gender, BMI and age.

Variables	Non-adjusted model		Gender, BMI and age adjusted model	
	β (95% CI)	*P* value	β (95% CI)	*P* value
VAS scores	1.168(0.954-1.305)	<0.001	0.860(0.722-1.041)	0.002
Lequesne index	1.097(0.892-1.191)	<0.001	0.855(0.691-1.073)	0.003

**Adjusted by gender, age and BMI; 95% CI: 95% Confidence interval.*

pg/ml vs 343.4±46.4 pg/ml, *P*=0.002; 383.5±53.1 pg/ml vs 316.0±64.6 pg/ml, *P*<0.001, respectively) (Figure 2A). However, no significant differences were observed regarding the serum CCL20 levels among the K-L grade subgroups (F=0.745, *P*>0.05) (Figure 2B). Moreover, serum CCL20 levels were not significantly correlated with SF CCL20 levels (r=0.051, *P*=0.960) (Figure 2C).

Association of CCL20 levels with clinical severity

To explore whether CCL20 levels are related to symptomatic severity, we recorded the VAS scores and Lequesne indexes and further investigated their correlation with the SF CCL20 levels in all knee OA patients. Accordingly, we found that the SF CCL20 levels were also positively correlated with the VAS score (r=0.362, *P*<0.001) (Figure 3A) and Lequesne indexes (r=0.340, *P*<0.001) (Figure 3B), indicating that CCL20 is involved in inflammation-related pain and functional impairment in knee OA. Further linear regression demonstrated that SF CCL20 levels were still significantly and positively associated with the VAS (β=0.860 95% CI:0.722-1.041; R=0.320; *P*=0.002) and Lequesne indexes (β=0.855, 95%CI: 0.691-1.073; R=0.300, *P*=0.003) after adjustment for gender, BMI and age (Table 2).

Discussion

The present study aimed to investigate the association of serum and SF CCL20/MIP-3α levels with disease severity in patients with primary knee OA. We demonstrated for the first time that SF but not serum CCL20/MIP-3α levels were independently and positively associated with radiographic progression and clinical symptoms. These correlations remained significant after adjustment for age and BMI (Table 2). These findings indicate that CCL20/MIP-3α may participate in the progression of primary knee OA in patients.

In recent years, biomarkers both in serum and in SF represent a group of potentially novel tools for use in addition to conventional diagnostic imaging examinations. Biomarkers are easily examined in office-based practices, allow disease activity to be objectively assessed, and even aid in predicting disease prognosis as well as evaluating treatment responses[24]. With regard to knee OA, using biomarkers both in serum and in SF could allow clinicians to monitor disease progression, predict prognosis and help inform treatment strategies[25]. For example, several adipocytokines, including leptin, adiponectin, ADAM metallopeptidase with thrombospondin type 1 motif 4 (ADAMTS-4) and aggrecan ARGS neo-epitope fragment (ARGS), and some inflammatory markers, including interleukin-6 (IL-6), interleukin-1β (IL-1β) and chemokine (CeC motif) ligand 3 (CCL3), have been implicated in OA progression[26,27].

CCL20/MIP-3α has been identified to play substantial roles in the progression of many inflammatory diseases. However, whether CCL20/MIP-3α levels are correlated with OA development has not been investigated. In this study, we first demonstrated that the SF CCL20/MIP-3α levels were positively and significantly correlated with the K-L grade, which provides strong evidence for the role that CCL20/MIP-3α plays in OA progression. In a previous study, CCL20 significantly increased the β-N-acetylhexosaminidase level in osteoblasts from patients with OA[28]; OA subchondral bone is characterized by fibrosis, and β-N-acetylhexosaminidase is an enzyme involved in the degradation of glycosaminoglycans and is highly expressed by osteosclerotic osteoblasts[29]. This work implied that CCL20 may be involved in subchondral bone sclerosis, a finding that requires further investigation. Additionally, CCL20 can lead to ECM-bone remodeling in OA[28] and is able to induce alkaline phosphatase only in osteogenic-induced mesenchymal stem cells[30], thus supporting the direct involvement of CCL20 during bone mineralization in OA.

We next investigated the relationship between CCL20/MIP-3α levels and clinical severity defined by the VAS score and Lequesne Algofunctional Index. We also found that SF CCL20/MIP-3α levels were positively associated with clinical severity. It has been shown that proinflammatory factors are released into the joint and that synovitis is highly correlated with OA pain[31]. Previous studies showed that CCL20 participates in the synovial inflammation process in diseases, including OA[32,33]. CCL20 mRNA was shown to be upregulated following surgery, resulting in postoperative pain, local inflammation, and tissue repair[34]. This finding may indicate that the involvement of CCL20/MIP-3α in radiographic progression may be associated with symptomatic severity in knee OA patients.

There were some inevitable limitations that should be taken into consideration. First, this cross-sectional study was carried out with a relatively small number of participants among a Chinese population. Therefore, a study in a larger population is warranted to verify our findings. Second, we did not measure CCL20/MIP-3α levels in SF samples from healthy individuals for ethical reasons. Third, we did not investigate

whether hyaluronic acid injection or surgery changes the SF levels of CCL20/MIP-3α in patients with knee OA. Fourth, we did not record the synovial effusion size or volume and did not investigate the relationship between CCL20 concentrations or K-L grade and effusion size, which may act as a confounder for increasing CCL20 levels. Finally, only the CCL20/MIP-3α levels were measured, and investigations of other potential chemokines may provide more useful information regarding OA development.

In summary, we found that SF but not serum CCL20/MIP-3α levels are related to the disease severity of primary knee OA. Whether interventions targeting CCL20/MIP-3α and its pathways has clinical application deserves further study.

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