Journal of Clinical Laboratory Analysis 30: 437–443 (2016)

Possible Involvement of Serum and Synovial Fluid Resistin in Knee Osteoarthritis: Cartilage Damage, Clinical, and Radiological Links

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Background: Resistin is an adipocytokine associated with inflammation and insulin resistance. Recent studies have shown that resistin plays an important role in the pathogenesis and progression in osteoarthritis (OA) patients. The current study was aimed at investigating the relationship between resistin in serum and synovial fluid (SF) and disease severity in patients with knee osteoarthritis. *Method:* Seventy-four patients diagnosed with knee OA and 79 healthy controls receiving regular body check in our hospital were recruited in the study. The Noyes score method was used to assess articular cartilage damage arthroscopically. The symptomatic severity was evaluated according to the Western Ontario McMaster University Osteoarthritis (WOMAC) scores. The radiographic disease severity of OA was assessed by the Kellgren-Lawrence (K–L) grading system. The resistin levels in serum and SF were determined by enzyme-linked immunosorbent assay. Cartilage degradation marker CTX–II in SF was also examined. *Results:* SF but not serum resistin levels are positively associated with Noyes scores, K-L grading scores WOMAC pain scores, physical functional scores and WOMAC total scores. In addition, SF resistin correlated positively with CTX-II. *Conclusion:* Resistin in SF might serve as a potential biomarker for reflecting the disease severity and cartilage degenerative extent of knee OA. J. Clin. Lab. Anal. **30**:437–443, 2016. © 2015 Wiley Periodicals, Inc.

Key words: osteoarthritis; resistin; disease severity; catilage damage

INTRODUCTION

Osteoarthritis (OA) is one of the most common degenerative joint diseases in aging population. It is characterized by articular cartilage destruction, osteophyte formation, and subchondral bone abnormalities (1). Epidemiological studies showed that around 15% of the world population (2) and 37% of people over 60 years (3) suffer from OA and the morbidity is estimated reaching 100,000 new cases per year (3). Osteoarthritis affects any articular with the knee joints most commonly involved (4). The increased OA morbidity calls for the urgency to make early diagnosis, prevention, and treatment. In recent years, biochemical markers represent a possible nonivasive method to assess the risk for the progression of the disease, detect

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Received 6 April 2015; Accepted 11 July 2015
DOI 10.1002/jcla.21876
Published online in Wiley Online Library (wileyonlinelibrary.com).

early changes of the disease and evaluate the response to such potential disease-modifying OA drugs (5, 6).

Adipocyte-derived molecules, also known as adipokines, have prompted much interest in OA pathogenesis studies over the past years in that they play crucial roles in bone and cartilage homeostasis (7, 8). In addition, the association of adipokines with obesity, along with their pro- or anti-inflammatory functions indicates that adipokines might represent another crucial mediators that links inflammation with obesity and OA (9, 10).

Resistin is a newly identified adipocytokine that has demonstrated links between obesity and insulin resistance in rodents (11). It is mainly expressed and secreted by adipose tissue, but has also been proved in other tissues in rodents (12). In contrast with animal models, immunocompetent cells rather than adipocytes seem to be the major source of resistin in humans that is in consistent with the phenomenon that proinflammatory properties of resistin are superior to its insulin resistance-inducing effects (13).

Recently, resistin has been investigated with its occurrence and potential involvement in the pathophysiology of OA. It is reported that injection of resistin into knee joints of healthy mice induced cartilage destruction and synovial inflammation (14). Morever, resistin could direct effect on cartilage matrix and cytokine production to upregulate expression of MMP-1, MMP-13 as well as IL-6 and TNF-alpha, etc. (15). In human studies, it has also been proved that synovial fluid and serum resistin levels increase in patients after knee injury (16). Resistin levels have also been identified elevated in both serum and synovial fluid in OA patients, indicating its role involved in inflammatory changes of OA (17,18). In a previous study, Koskinen et al. found levels of resistin synovial fluid are positively associated with IL-6 and matrix metalloproteinases MMP-1, MMP-3 in knee OA patients (19).

All these data indicate that resistin may play crucial roles in OA progression. However, to our knowledge, there have been no studies available illustrating the correlation between serum and SF concentrations of resistin and disease severity as well as degree of cartilage degeneration in knee OA patients. Therefore, the present study was carried out to explore whether serum and SF levels of resistin are related to the disease severity and extent of cartilage injury of the disease.

MATERIALS AND METHODS

Patients and Controls

This study was approved by the ethical committee of the Second Hospital of Hebei Medical University and performed in conformity with the declaration of Helsinki principles. Written informed consent was obtained from all participants. Seventy-four patients with primary knee OA visited our hospital undergoing arthroscopic irrigation and debridement from July 2014 to March 2015 were enroll in the present study. All patients met the American College of Rheumatology criteria for the diagnosis of OA. The **criteria** are: patients suffer articular knee pain with at least three of the below items: (1) Active joint motion with crepitus, (2) morning stiffness no more than half an hour, (3) age >50 years, (4) bony enlargement of the knee on examination, and (5) bony tenderness of the knee (6). No palpable warmth. **Laboratory criteria:** (1) Erythrocyte sedimentation rate (ESR) < 40 mm/h, (2) rheumatoid factor (RF) < 1:40, and (3) synovial fluid analysis: clear, viscous, white blood cell count < 2000/μL. **Radiographic criteria**: Presence of osteophytes. Seventy-nine sex and age matched healthy individuals receiving routine body check in our hospital during the same period were recruited as controls. All the controls had no signs of OA-related symptoms and radiographic changes. Participants were excluded if they suffer from knee injury, joint infection, secondary posttraumatic arthritis, systemic inflammatory, or rheumatoid disorders, malignant disease, progressive renal disease, gout, hydroxyapatite, or calcium pyrophosphate deposition disease. In addition, patients were also excluded if any anti-inflammatory drugs, corticosteroids as well as sodium hyaluronate were used within the past 2 weeks.

Definition of Cartilage Damage

Noyes method (20) was utilized to evaluate articular cartilage damage arthroscopically while performing arthroscopic irrigation and debridement. This rating system was based on depth and area of cartilage damage. Cartilage damage < 10 mm in diameter is regarded clinically insignificant and marked 0 points. One point is designated if the diameter of cartilage damage ranges from 10 to 15 mm. Two points are given for an open lesion less than 50% thickness, three points are given for an open lesion more than 50% thickness of the articular cartilage and 5 points are given for bone exposure. If the cartilage damage is > 15 mm in diameter, twice the number of points are assigned as for damage 10–15 mm in diameter. The knee is divided into six anatomical areas: medial femur, medial tibia, lateral femur, lateral tibia, patella, and femoral sulcus. After evaluating cartilage damage in each area, patellofemoral, medial tibiofemoral, and lateral tibiofemoral compartment scores are calculated. The total scores were then expressed as a percent of normal using a standard formula. We used the sum of the scores for each part for convenience. All arthroscopic operations and evaluation were performed by one expert in our hospital.

Definition of Disease Severity

The symptomatic severity of OA was assessed by the Western Ontario McMaster University Osteoarthritis Index (WOMAC) including three subscales (21): pain, stiffness, and physical function. The psychometric properties of the WOMAC score have been shown to be valid and reliable in patients with primary knee OA (22, 23).

Antero-posterior weight-bearing radiographs of both knees were taken before the operation (24). Radiographic severity was evaluated according to the Kellgren–Lawrence grading system: Grade 1, doubtful narrowing of joint space and possible osteophytic lipping; Grade 2, definite osteophytes and possible narrowing of joint space; Grade 3, moderate multiple osteophytes, definite narrowing of joints space, some sclerosis and possible deformity of bone contour; Grade 4, large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour (25). The grade used for analysis was the higher of the two knees. The scores of radiographs were assessed by an experienced radiologist in our hospital who was blinded to the selection of subjects.

TABLE 1. Baseline Characteristics

	OA patients ($n = 74$)	Healthy controls ($n = 79$)	P value
Age (Y)	65.8 ± 7.3	66.2 ± 6.9	0.451
Gender (F/M)	40/34	42/37	0.298
BMI (kg/m^2)	26.7 ± 1.5	26.8 ± 1.2	0.353
Diabetes suffering (Yes/No)	17/57	/	
WOMAC pain scores	9 (4–17)	/	
WOMAC stiffness scores	5 (2–8)	/	
WOMAC physical function scores	43 21–66)	/	
WOMAC total scores	61 (29–90)	/	
Noyes scores	11 (2–36)	/	
KL grading (2/3/4)	22/29/23	/	
Serum resistin levels (ng/ml)	19.5 (10.2–36.7)	17.2 (8.79–32.1)	0.035
SF resistin levels (ng/ml)	8.7 (2.7–15.6)	/	

Basic values are expressed as the mean value ± SD or n (%). WOMAC index, Noyes scores and serum/SF resistin levels were given as median (interquartile range).

ELISA

Synovial fluid was aspirated from the affected knee using sterile knee puncture just before the arthroscopic irrigation and debridement was performed, centrifuged to remove cells and joint debris and stored immediately at –80°C until the day of measurement. Each synovial fluid sample from patients was observed by two experienced pathologists in our hospital to decide whether abnormal deposits were existed. No synovial fluid was extracted from the controls due to ethical concerns. Venous blood samples were obtained from the same patients on the day of arthroscopic operation and all healthy individuals receiving regular physical examination. The specimen were then centrifuged and stored at –80°C until utilized. Double-blind quantitative analysis of resistin in serum and synovial fluid was performed by sandwich enzyme-linked immunosorbent assay (ELISA) using a commercially kit according to the manufacturer's protocol (Santa Cruz Biotechnology, Santa Cruz, USA). SF CTX-II levels were also examined with the same procedure (Santa Cruz Biotechnology, Santa Cruz, USA).

Statistic Analysis

Resistin concentration, WOMAC scores, and Noyes scores were expressed as median (range) whereas the basic clinical data from participants were expressed as mean ± SD. Serum resistin levels between OA patients and controls were analyzed using unpaired Student's t test. The correlation of serum or SF resistin concentrations with WOMAC scores, Noyes scores, or levels of CTX-II was determined by Pearson or Spearman correlation analysis, where appropriate. $P < 0.05$ was considered significant.

RESULTS

Basic Clinical Data

Characteristics of the study population are demonstrated in Table 1. There are no clinical meaningful differences between OA patients and controls in age (65.8 ± 7.3 years vs. 66.2 ± 6.9 years, $P = 0.451$), gender (40/34 vs. 42/37 F/M, Chi-square $P = 0.298$), or body mass index (26.7 ± 1.5 kg/m^2 vs. 26.8 ± 1.2 kg/m^2, $P = 0.353$).

Resistin levels in serum and SF

Serum fluid resistin expression of knee OA patients and controls was also showed in Table 1. Compared with healthy controls, knee OA patients had a slightly higher level of resistin concentration in serum [19.5 10.2–36.7)ng/ml vs. 17.2 8.79–32.1)ng/ml, $P = 0.035$]. The serum levels of resistin were considerably higher compared to the SF levels [19.5 10.2–36.7)vs. 8.7 2.7–15.6) ng/ml, $P < 0.001$)] (Table 1).

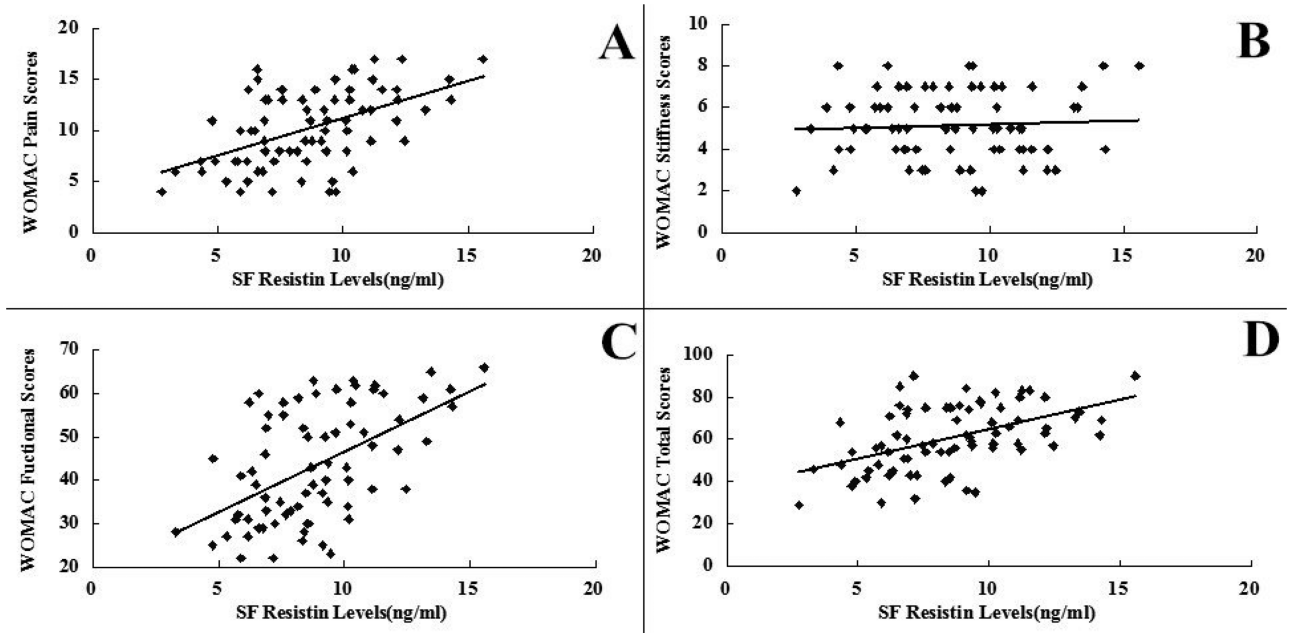

Fig. 1. Correlation of SF resistin levels (ng/ml) with WOMAC pain (A), stiffness (B), physical function (C), and total (D) scores in OA patients.

Association between serum and SF resistin levels and disease severity

SF levels of resistin were positively associated with the radiographic severity of knee OA ($r = 0.642$, $P < 0.001$) (Fig. 3). In addition, SF concentrations of resistin were positively correlated with WOMAC pain ($r = 0.514$, $P < 0.001$) (Fig. 1A), WOMAC function ($r = 0.533$, $P < 0.001$) (Fig. 1B) and WOMAC total scores ($r = 0.491$, $P < 0.001$) (Fig. 1D). However, the correlation between SF resistin levels and WOMAC stiffness scores did not reach significance($r = 0.066$, $P > 0.05$) (Fig. 1C). And we surprisingly found, there were no significant associations between

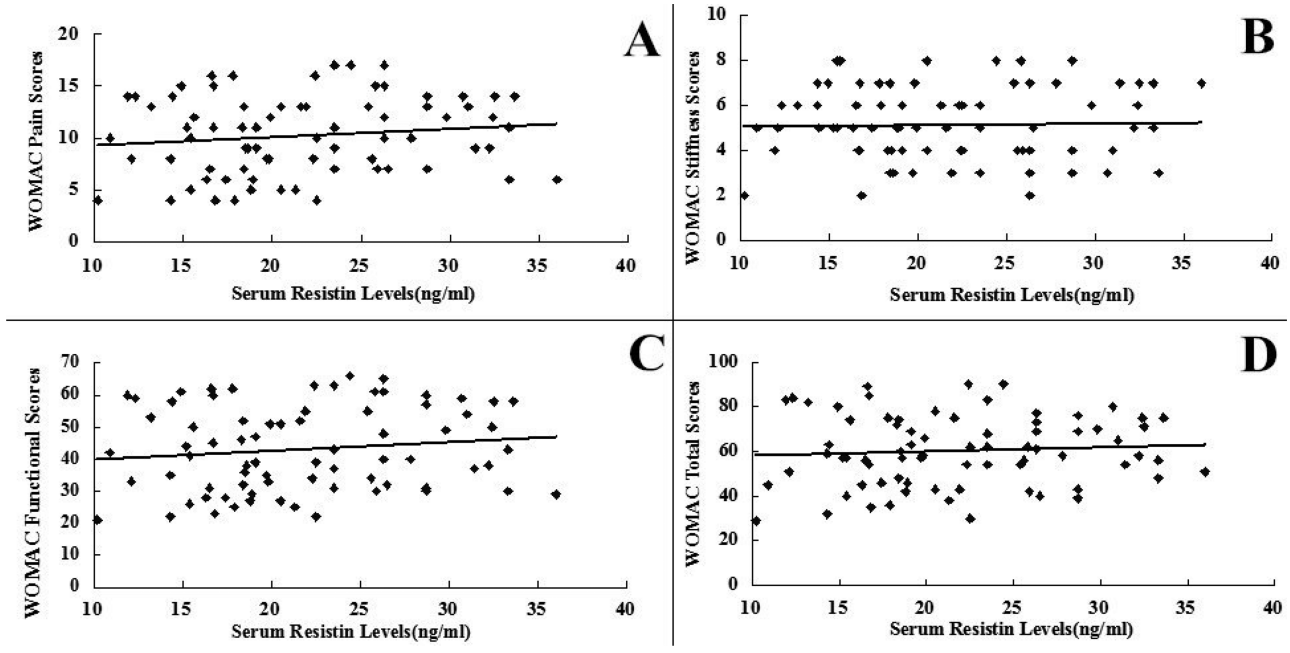

Fig. 2. Correlation of serum resistin levels (ng/ml) with WOMAC pain (A), stiffness (B), physical function (C), and total (D) scores in knee OA patients.

TABLE 2. Multivariate Linear Regression

	(WOMAC P)		(WOMAC S)		(WOMAC F)		(WOMAC T)	
	β	*P*	β	*P*	β	*P*	β	*P*
Age	**−0.035**	**0.810**	**−0.027**	**0.854**	**−0.056**	**0.732**	**-0.041**	**0.772**
BMI	**0.126**	**0.142**	**0.142**	**0.117**	**0.156**	**0.101**	**0.130**	**0.138**
Gender	**0.079**	**0.31**	**0.085**	**0.294**	**0.053**	**0.734**	**0.064**	**0.661**
Diabetes suffering	**0.096**	**0.188**	**0.092**	**0.190**	**0.051**	**0.740**	**0.083**	**0.298**
SF resistin	**1.663**	**0.001**	**0.127**	**0.142**	**1.746**	**0.001**	**1.528**	**0.001**
Serum resistin	**0.053**	**0.733**	**0.031**	**0.818**	**0.067**	**0.667**	**0.058**	**0.728**

WOMAC P/S/F/T = WOMAC pain/stiffness/functional/total.

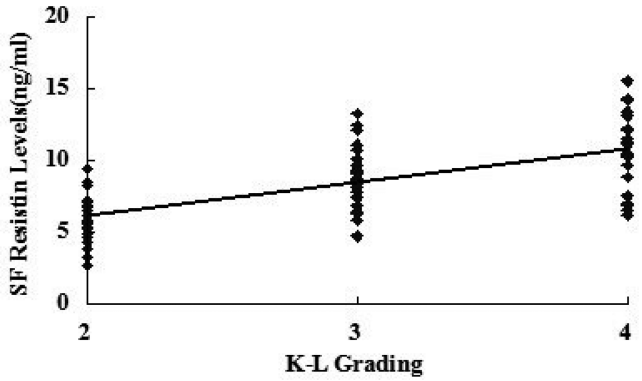

Fig. 3. Correlation of SF resistin levels (ng/ml) in knee OA patients with radiographic severity measured by K–L grading scale.

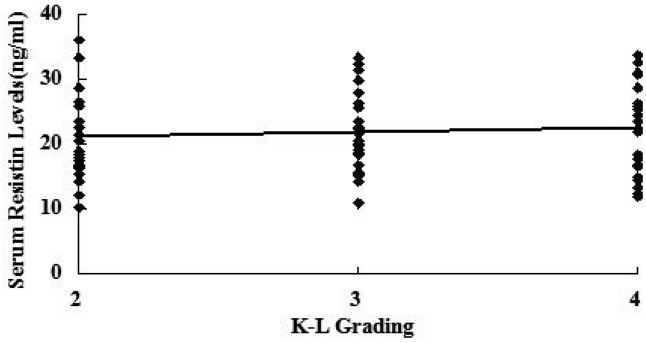

Fig. 4. Correlation of SF resistin levels (ng/ml) in knee OA patients with radiographic severity measured by K–L grading scale.

serum resistin concentrations and WOMAC subscale or total scores ($P < 0.05$) as well as K-L Grading system in OA patients ($P < 0.05$) (Figs. 2 and 4).The correlation between serum and SF resistin levels and WOMAC scores was further evaluated by multinomial logistic regression analysis. Multiple regression analysis showed that the correlation between SF resistin concentrations and WOMAC scores was still significant after adjusting for other confounding factors (Table 2.

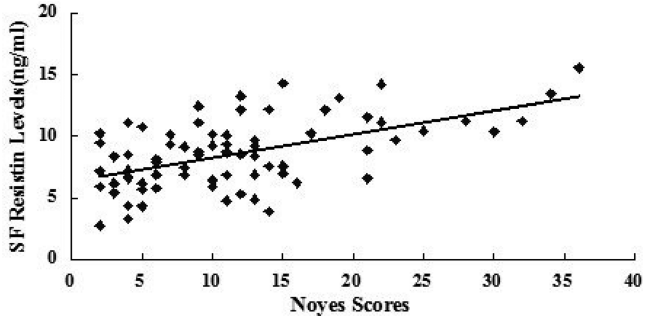

Fig. 5. Correlation of SF resistin levels (ng/ml) in knee OA patients with cartilage damage extent according to Noyes scores.

Association between synovial fluid resistin levels and cartilage damage degree

In order to identify the role that resistin plays in the cartilage damage process, we explored the relationship between synovial fluid resistin levels and Noyes rating scores as well as cartilage degeneration mark CTX-II. Interestingly, we found synovial fluid resistin concentrations were positively correlated with Noyes scores ($r = 0543$ $P < 0.001$) and CTX-II ($r = 0.411$, $P = 0.001$) (Figs. 5 and 6).

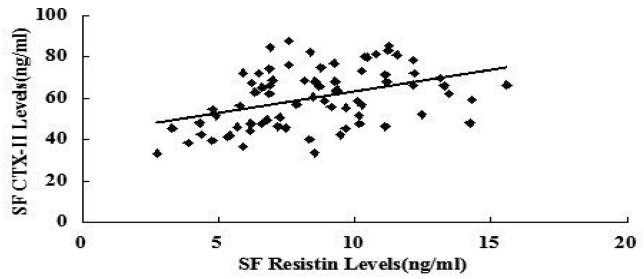

Fig. 6. . Correlation of SF resistin levels (ng/ml) in knee OA patients with SF CTX-II levels.

DISCUSSION

The current study investigated the relationship between resistin expression in SF and serum and disease severity as well as cartilage damage degree. Notably for the first time, in SF instead of serum, positive correlations were found between resistin and the Noyes Scores, SF CTX-II concentrations as well as K-L Radiographic Grading, WOMAC pain, WOMAC Functional and WOMAC total scores. These results indicate that resistin in SF plays an important role in the progression of knee OA and may serve as a novel and reliable biomarker for reflecting disease severity and cartilage degree.

Osteoarthritis (OA) is a debilitating degenerative joint disease particularly affecting weight-bearing joints within the body, principally the knees. In recent years, biochemical markers show promise in determination of the disease severity and monitoring of the efficacy and safety of disease-modifying OA drugs, with the potential to act as diagnostic and prognostic tools (26). The presence of local joint inflammation and altered cartilage and bone turnover in OA implicates a potential role for a range of biomarkers in OA progression.

Adipokines are protein mediators secreted by adipose tissue. Recently, adipokines have also been involved in the regulation of inflammation and catabolic process of in various arthritis including osteoarthritis (27,28). Resistin, known as one of adipocyte-secreted factors (ADSF), was proposed as a potential link between obesity and diabetes (29). It has been proved that resistin in humans is synthesized predominantly by mononuclear cells both within and outside adipose tissue (13). Recently, the involvement of resistin in bone metabolism has been widely studied. Resistin could upregulate expression of MMP-1, MMP-13, and ADAMTS-4 in human articular chondrocytes (16). Furthermore, resistin is capable of stimulating proteoglycan degradation, as well as inhibiting the production of proteoglycan and type II collagen in mouse and human cartilage explants (16).

In the present study, serum resistin levels were found significantly higher than matched synovial levels, which is consistent with the previous study (30). Most controversial studies focused on the relationship between systemic resistin concentration and hand OA. One study showed serum resistin levels was associated with radiographic subchondral erosion in patients suffering from hand OA (31). However, resistin was not correlated with radiographic progression in hand OA in another small cross-sectional study (32). In our study, the correlation between serum levels of resistin and radiographic, cartilage damage, and WOMAC scores in knee OA did not reach significance, indicating that hand osteoarthritis tends to be systemic whereas the involvement of resistin in knee OA is local and the pathological process is probably taken place in the joint. This implicates that resistin could be locally released and may participate the inflammation process merely within the articular joint.

In contrast with the serum resistin, we notably found that elevated resistin concentrations in SF were positively related to greater pain and worse physical disability in OA patients. In addition, increased SF resistin levels also correlated with cartilage damage defined by Noyes scores, SF levels CTX-II as well as K-L Grading. This result is concordant with a previous study that SF resistin concentration is associated with inflammation markers IL-6 and matrix metalloproteinases MMP-1, MMP-3 in knee OA patients (19). In a respective study, SF resistin levels are positively associated with systemic markers of inflammation (33). It should be noted that levels of resistin in the OA synovial fluid was significant lower than in matched OA serum levels in that resistin is widely secreted in various organs as mentioned above.

There several limitations should be taken into account. First, the sample size was relatively small among Chinese individuals. Further multicentral study in a larger sample is required to identify the results. Second, this study was cross-sectional; therefore, our findings should be validated in long-term prospective studies. Third, we only examed resistin, which is one of the adipokines involved in the progression of OA, other biomarkers like leptins and adiponectin as well as their correlations with OA deserve further intensive study. Last, we did not examine the resistin levels after arthroscopic operations.

In summary, patients with primary knee OA had elevated levels of serum resistin compared with healthy controls. We further performed this study aiming at relating serum and SF levels of resistin to the disease severity knee OA. We demonstrated that SF but not serum resistin concentrations significantly correlated with the magnitude of OA radiographic progression and symptomatic severity as well as cartilage damage. Resistin in SF measurement may serve as a novel biochemical marker of disease progression with the potential to contribute to the fundamental processes underlying the pathogenesis of knee OA. Further intensive studies are warranted to elucidate the influence of resistin on disease outcome.

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