Radiographic Bone Damage in Chronic Gout Is Negatively Associated with the Inflammatory Cytokines Soluble Interleukin 6 Receptor and Osteoprotegerin

JUNG-YOON CHOE, GEON HO LEE, and SEONG-KYU KIM

ABSTRACT. ***Objective.*** We investigated the risk factors for radiographic bone damage to foot joints in patients with chronic gout among various patient characteristics and serum inflammatory cytokines such as interleukin 1ß (IL-1ß), IL-6, soluble IL-6 receptor (sIL-6R), osteoprotegerin (OPG), and receptor activator of nuclear factor-κB ligand (RANKL).

Methods. Fifty consecutive male patients with gout and 54 age-matched healthy male controls were enrolled. Serum levels of cytokines including IL-1ß, IL-6, sIL-6R, OPG, and RANKL were measured using ELISA. Radiographic damage indices including erosion scores, narrowing scores, and total scores for foot joints were assessed according to a modified Sharp-van der Heijde system.

Results. There were significant differences in serum IL-1ß, IL-6, sIL-6R, OPG, and RANKL levels between patients with gout and the controls, after adjustment for confounding factors such as age, body mass index, blood urea nitrogen, creatinine, triglyceride, and fasting blood glucose ($p = 0.034$ for IL-1ß, $p < 0.001$ for IL-6, $p = 0.040$ for sIL-6R, $p = 0.002$ for OPG, and $p = 0.018$ for RANKL). Radiographic damage indices (erosion, narrowing, and total scores) were negatively associated with serum sIL-6R and OPG levels in multivariable-adjusted regression analysis. Serum sIL-6R levels in patients without radiographic damage were higher than in those with damage ($p = 0.006$).

Conclusion. Radiographic damage in patients with chronic gouty arthritis was negatively associated with serum sIL-6R and OPG. Further study on the role of inflammatory cytokines in the pathogenesis of radiographic damage in gout is needed. (J Rheumatol First Release Dec 15 2010; doi:10.3899/jrheum.100727)

Key Indexing Terms:
GOUT RADIOGRAPHIC DAMAGE INTERLEUKIN 1ß INTERLEUKIN 6
SOLUBLE INTERLEUKIN 6 RECEPTOR OSTEOPROTEGERIN RANKL

Gout is one of the most common arthropathies and is caused by microcrystal deposition around and in joints and soft tissues[1,2]. Well demarcated paraarticular bone erosion with overhanging edges has been recognized as a radiographic characteristic in established gout[3]. Additional features, including punctate bony calcifications, osteopenia, and intraosseous deposition of tophi, have also been noted in gout.

Triggering and amplification of intense inflammation in the joint cavity by monosodium urate (MSU) are typically present in gouty arthritis. However, the pathogenic mechanism of bony damage in crystal-induced arthropathies including gout and pseudogout has still not been established. Microcrystals downregulate bone formation and induce bone resorption in human osteoblastic cells[4]. A recent study has shown that enhanced osteoclastogenesis in patients with tophaceous gout is supported by higher circulating levels of receptor activator of nuclear factor-κB ligand (RANKL), increased recruitment of osteoclast-like cells within tophi of affected joints, and reduced expression of osteoprotegerin (OPG) from synoviocytes[5]. In addition, interleukin 1ß (IL-1ß) is now considered a crucial cytokine in the development and progression of gouty inflammation due to MSU crystals[6,7,8]. Expressions of IL-6 and soluble IL-6 receptor (sIL-6R) are significantly increased in the synovial fluid and blood of patients with gout[9,10]. In addition to the functional disturbances of RANKL and OPG related to osteoclast activity, these inflammatory cytokines, including IL-1ß, IL-6, and sIL-6R, are well known as important mediators, inducing both activity and formation of osteoclasts[11,12].

There is not sufficient data regarding risk factors related to

From the Department of Internal Medicine, Arthritis and Autoimmunity Research Center, and the Department of Family Medicine, Catholic University of Daegu School of Medicine, Daegu, South Korea.

J-Y. Choe, MD, PhD, Professor, Department of Internal Medicine, Arthritis and Autoimmunity Research Center; G.H. Lee, MD, PhD, Assistant Professor, Department of Family Medicine; S-K. Kim, MD, PhD, Associate Professor, Department of Internal Medicine, Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine.

Address correspondence to Dr. S-K. Kim, Department of Internal Medicine, Arthritis and Autoimmunity Research Center, Catholic University of Daegu School of Medicine, 3056-6 Daemyung 4-Dong, Namgu, Daegu 705-718, South Korea. E-mail: kimsk714@cu.ac.kr

Accepted for publication October 29, 2010.

radiographic damage in chronic gout. Our hypothesis is that inflammatory cytokines such as IL-1ß, IL-6, sIL-6R, OPG, and RANKL as well as various patient characteristics might be risk factors for radiographic bone damage in gout.

MATERIALS AND METHODS

Subjects and data collection. Patients were consecutively recruited from the rheumatic disease outpatient clinic at Daegu Catholic University Medical Center, Daegu, South Korea. All were men. They fulfilled preliminary classification criteria for gout proposed by Wallace, *et al*[13]. Age-matched male controls were also enrolled from the Health Promotion Center at the same medical center. They did not have a personal or family history of gout or any form of arthritis. Informed consent was obtained from members of both study groups.

Patient characteristics data, including age at time of study, age at onset of disease, body mass index (BMI), disease duration, and medications for gout, were collected from review of medical records and individual interview. Medications for gout management were reviewed. Peripheral venous blood after a fasting time of about 8 h was sampled from patients with gout and from controls, and then centrifuged at 980 ×g for 15 min. The serum samples were stored at –80°C until analysis. Erythrocyte sedimentation rate (ESR) was measured by Westergren method at the time of blood sampling. We measured blood urea nitrogen (BUN), creatinine, triglyceride, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and fasting blood glucose.

Measurements of inflammatory cytokines using ELISA. Serum IL-6, sIL-6R, and OPG in patients with gout were measured by DuoSet ELISA Development Kit (R&D Systems, Minneapolis, MN, USA). The IL-1ß kit is a solid-phase sandwich ELISA (Invitrogen Corp., Carlsbad, CA, USA), and RANKL in patients with gout was measured by ELISA kit (Usen Life Science, Wuhan, China).

The 96-well microplate with 100 μl per well of 2 μg/ml mouse anti-human capture antibody was incubated overnight at room temperature. After incubation, block plates of 1% bovine serum albumin were placed in phosphate buffered saline (PBS) for 1 h at room temperature. The human standard protein or samples were added (100 μl) and incubated 2 h at room temperature. Then 400 μl 0.05% Tween 20 in PBS was added, and each well was washed 3 times. One hundred microliters of mouse anti-human biotinylated detection antibody 2 μg/ml with plates was incubated 2 h at room temperature. Streptavidin-horseradish peroxidase 1:200 was diluted to each well for 20 min at room temperature. A color reagent A (H_2O_2) and color reagent B (tetramethylbenzidine) substrate solution was stopped after 20 min with 2 N H_2SO_4. Then each well was immediately measured in a microplate reader at a wavelength of 450 nm.

Repeatability assay for inflammatory cytokines measured in our study was assessed by intraclass correlation coefficient (ICC). The calculation of ICC was done in 54 controls. The values of ICC for each cytokine were as follows: 0.97 for IL-1ß, 0.95 for IL-6, 0.99 for sIL-6R, 0.88 for OPG, and 0.98 for RANKL.

Measurement of radiographic joint damage. The radiographic damage of foot joints was assessed using a modified Sharp-van der Heijde system suggested by Dalbeth, *et al*[14]. Radiographs of both anteroposterior and oblique views of the feet were obtained. The Sharp-van der Heijde erosion score (0–5) and its joint space narrowing score (0–4) for each joint were assessed by 2 rheumatologists. Combined scores of erosion and joint space narrowing were also obtained to determine the total damage index.

Statistical analysis. Data were described as mean ± SD and number (percentage of total). The distribution of data was verified by normality test using Kolmogorov-Smirnov and Shapiro-Wilk tests. Variables for inflammatory cytokines and other sequential measurements were not equally distributed. Statistical association between inflammatory cytokines and patient/radiographic measurements were assessed using Spearman's correlation analysis. Comparison for the differences of sequential variables between the 2 groups was performed using the Mann-Whitney U test. ANCOVA was applied to determine the differences in inflammatory cytokines using different measurements between controls and patients. Association analysis for scores of radiographic damage indices including erosion, narrowing, and total scores was performed by multivariable-adjusted regression analysis. A p value < 0.05 was considered statistically significant. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics and inflammatory cytokine profiles of study subjects. We enrolled patients with gout (n = 50) and age-matched healthy controls (n = 54; Table 1). Some clinical and laboratory measurements including BMI, BUN, creatinine, triglyceride, and fasting blood glucose were statistically different between the 2 groups in comparison to general characteristics. Medications used for gout and radiographic damage indices are also listed in Table 1.

We compared serum levels of inflammatory cytokines such as IL-1ß, IL-6, sIL-6R, OPG, and RANKL in patients with gout with levels in controls (Figure 1). Serum IL-1ß, IL-6, sIL-6R, and RANKL levels in patients with gout were significantly higher than those in healthy controls, after application of ANCOVA method to adjust for confounding factors such as age, BMI, BUN, creatinine, triglyceride, and fasting blood glucose: 30.1 ± 61.4 vs 0.8 ± 2.7 pg/ml (p_{adj} = 0.034) for IL-1ß; 240.9 ± 279.1 vs 7.1 ± 8.8 pg/ml (p_{adj} < 0.001) for IL-6; 158.3 ± 170.8 vs 76.3 ± 80.8 ng/ml (p_{adj} = 0.040) for sIL-6R; and 118.4 ± 148.0 vs 40.6 ± 71.2 pg/ml (p_{adj} = 0.018) for RANKL, respectively). In addition, serum OPG levels were significantly lower in patients with gout than in controls: 729.0 ± 685.4 vs 1745.2 ± 1575.6 pg/ml (p_{adj} = 0.002).

Association of radiographic damage indices with patient/laboratory measurements and inflammatory cytokines. Simple correlation analysis revealed that older patients and patients with higher ESR levels showed higher radiographic erosion scores (r = 0.321, p = 0.023; and r = 0.377, p = 0.007, respectively; Table 2). The radiographic narrowing score was negatively associated with BMI (r = –0.324, p = 0.036). Serum OPG levels were significantly related with sIL-6R levels (r = –0.693, p < 0.001). There was a positive correlation between IL-1ß and IL-6 levels in patients with gout (r = 0.378, p = 0.007). However, this analysis did not show any correlation between inflammatory cytokines and radiographic damage indices. Neither the OPG/IL-1ß ratio nor the RANKL/OPG ratio were related with all radiographic damage indices (data not shown). Serum uric acid levels showed close correlation with serum RANKL levels (r = 0.310, p = 0.029). Urate-lowering agents such as allopurinol and benzbromarone had no effect on the radiographic damage indices (data not shown). Serum IL-1ß, IL-6, OPG, and RANKL levels were similar between the absence (n = 32) and presence (n = 18) of radiographic damage (p > 0.05; Figure 2). In contrast, higher sIL-6R levels in patients without damage were noted, compared to patients with radiographic damage (p = 0.006). In

Table 1. General characteristics of patients with gout and healthy controls. Values are mean ± SD unless otherwise indicated.

Characteristic	Gout (n = 50)	Controls (n = 54)	p†
Age, yrs	44.2 ± 7.6	43.6 ± 6.3	NS
Disease duration, yrs	7.6 ± 6.6		
Age at onset, yrs	37.7 ± 7.2		
Body mass index, kg/m^2	26.0 ± 3.3	24.5 ± 2.6	0.012
Blood urea nitrogen, mg/ml	16.9 ± 5.7	14.1 ± 3.2	0.015
Creatinine, mg/ml	1.1 ± 0.2	1.0 ± 0.1	0.004
Uric acid, mg/ml	6.3 ± 2.2	6.3 ± 1.4	NS
Triglyceride, mg/ml	193.1 ± 92.4	149.1 ± 91.2	0.005
Total cholesterol, mg/ml	196.0 ± 38.5	201.6 ± 36.9	NS
HDL-C, mg/ml	48.5 ± 12.0	50.1 ± 14.6	NS
LDL-C, mg/ml	129.3 ± 35.2	131.7 ± 31.9	NS
Fasting blood glucose, mg/ml	97.8 ± 14.7	89.1 ± 17.4	0.001
Erythrocyte sedimentation rate, mm/h	9.4 ± 10.6	7.5 ± 5.1	NS
Patients with tophi, n (%)	9 (18.0)		
Radiographic damage indices			
Erosion score (0–5)	0.7 ± 1.2		
Narrowing score (0–4)	0.8 ± 1.0		
Total damage score (0–9)	1.6 ± 2.1		
Patients with radiographic damage, n (%)	18 (36.0)		
Medications, n (%)			
Allopurinol	30 (60.0)		
Benzbromarone	24 (48.0)		
Colchicine	46 (92.0)		
NSAID	44 (88.0)		

† Comparison between the 2 groups by Mann-Whitney U test. HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; NSAID: nonsteroidal antiinflammatory drug; NS: not significant.

addition, we could not find significant differences among inflammatory cytokines according to the presence (n = 9) or absence (n = 41) of tophi (p > 0.05 of all cytokines).

We assessed the effects of inflammatory cytokines on radiographic damage in gouty foot joints using multivariable-adjusted regression analysis. After adjustment for age, BMI, ESR, and inflammatory cytokines, all radiographic damage indices (erosion, narrowing, and total scores) in patients with gout were negatively associated with some inflammatory cytokines such as sIL-6R and OPG (Table 3). Clinical measurements and patient characteristics including age, BMI, and ESR were not related to radiographic damage.

DISCUSSION

Chronic gout is characterized by diverse radiographic features including bony destruction and extensive osteolytic lesions[5]. Until now, a definite pathogenic mechanism of structural bone damage has not been established, although MSU might be involved in the bone destruction of affected joints. Therefore, we aimed to identify the risk factors of radiographic damage in foot joints of patients with gout. We assessed patient characteristics and clinical and laboratory measurements as well as serum inflammatory cytokines such as IL-1ß, IL-6, sIL-6R, OPG, and RANKL. In addition, we assessed radiographic damage indices including joint erosion scores and joint narrowing scores. Our study demonstrates that inflammatory cytokines such as IL-1ß, IL-6, sIL-6R, OPG, and RANKL were significantly increased in patients with gout compared to age-matched healthy controls, and also that radiographic damage in patients with gout was negatively associated with inflammatory cytokines such as sIL-6R and OPG.

There is relatively little information on the molecular mechanism of bony damage in gout. Recently, Dalbeth, *et al* demonstrated the presence of numerous osteoclast-like cells around tophi or in the joints of tophaceous gout with bony erosion, as well as demonstrating that MSU crystals inhibited expression of OPG, a protective gene for osteoclastogenesis, in synovial fibroblasts[5]. Dalbeth, *et al* also showed that serum RANKL concentrations were significantly associated with radiographic erosion scores, and suggested that osteoclastogenesis contributed to the bone damage in chronic tophaceous gout. A recent study by Nguyen, *et al* reported that the fragility of bones in patients with tophaceous gout was associated with an imbalance between bone formation and absorption[15]. In our study, significantly higher expression of RANKL and lower expression of OPG in gout than in controls is compatible with findings reported by Dalbeth, *et al*[5]. In addition, patients with higher radiographic damage scores (erosion, joint narrowing, and total score) showed significantly lower serum OPG levels, while RANKL levels were not associated with damage scores. We did not show the differences of both RANKL and OPG levels according to the presence and

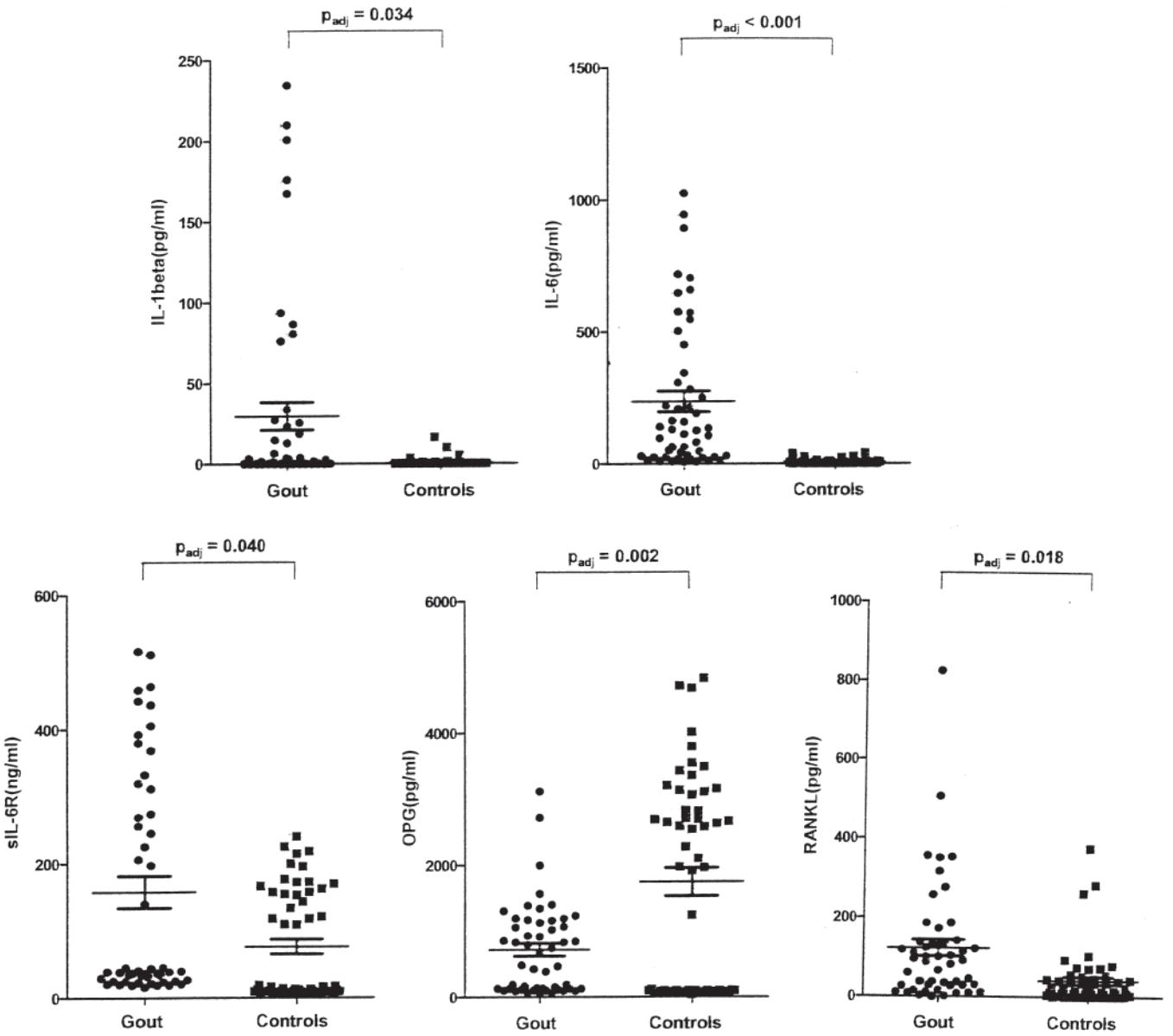

Figure 1. Comparison of serum interleukin (IL)-1ß, IL-6, soluble IL-6 receptor (sIL-6R), osteoprotegerin (OPG), and receptor activator of nuclear factor-κB ligand (RANKL) levels between gout and healthy controls. Significant differences of serum IL-1ß, IL-6, sIL-6R, OPG, and RANKL levels between 2 groups after adjusting for covariants such as age, body mass index, blood urea nitrogen, creatinine, triglyceride, and fasting blood glucose ($p = 0.034$, $p < 0.001$, $p = 0.040$, $p = 0.002$, and $p = 0.018$, respectively).

Table 2. Simple correlation analysis of radiographic damage indices with clinical/laboratory measurements and serum inflammatory cytokines in gout (Spearman's correlation).

Measure	Radiographic Joint Erosion Scores	Radiographic Joint Narrowing Scores	Osteoprotegerin	IL-1ß
Age	r = 0.321, p = 0.023	r = 0.229, p = 0.110	r = 0.235, p = 0.131	r = –0.012, p = 0.935
BMI	r = –0.288, p = 0.064	r = –0.324, p = 0.036	r = –0.142, p = 0.369	r = 0.004, p = 0.980
ESR	r = 0.377, p = 0.007	r = 0.133, p = 0.359	r = 0.143, p = 0.321	r = –0.097, p = 0.505
sIL-6R	r = –0.018, p = 0.903	r = –0.144, p = 0.318	r = –0.693, p < 0.001	r = –0.105, p = 0.331
IL-6	r = –0.039, p = 0.790	r = 0.071, p = 0.623	r = 0.089, p = 0.539	r = 0.378, p = 0.007
RANKL	r = 0.119, p = 0.410	r = –0.031, p = 0.833	r = –0.150, p = 0.299	r = 0.111, p = 0.441

IL-1ß: interleukin 1ß; IL-6: interleukin 6; sIL-6R: soluble IL-6 receptor; RANKL: receptor activator of nuclear factor-κB ligand; BMI: body mass index; ESR: erythrocyte sedimentation rate.

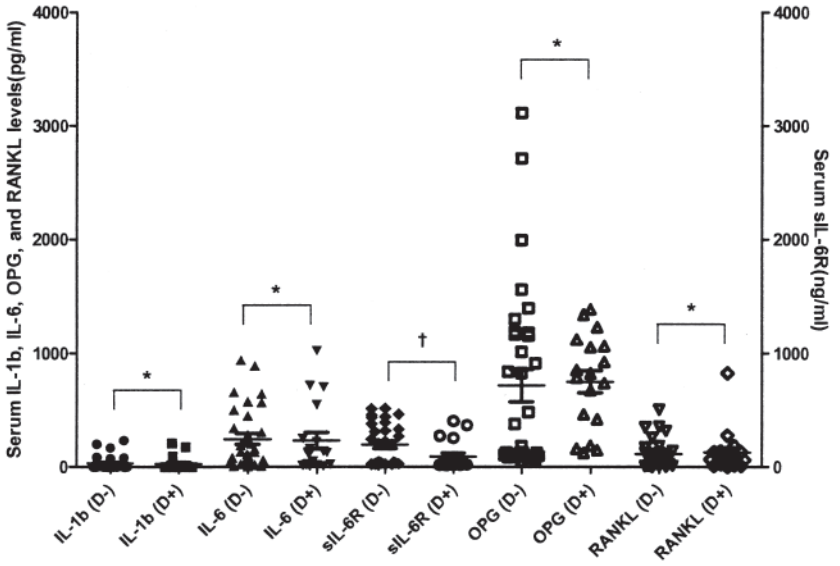

Figure 2. Comparison of expressions of inflammatory cytokines according to the presence/absence of radiographic damage in gout. D-: absence of radiographic damage; D+: presence of radiographic damage; IL-1ß: interleukin 1ß; IL-6: interleukin 6; sIL-6R: soluble IL-6 receptor; OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor-κB ligand. * $p > 0.05$. † $p = 0.006$.

Table 3. Multivariable-adjusted regression analysis for determining risk factors for radiographic damage indices.

Confounding Factors	Radiographic Joint Erosion Scores ß	p	95% CI for B (lower, upper bound)	Radiographic Joint Narrowing Scores ß	p	95% CI for B (lower, upper bound)	Total Radiographic Damage Scores ß	p	95% CI for B (lower, upper bound)
Age	0.280	0.122	–0.008, 0.068	0.322	0.064	–0.002, 0.054	0.313	0.073	–0.006, 0.118
BMI	–0.257	0.093	–0.205, 0.017	–0.176	0.221	–0.131, 0.031	–0.233	0.111	–0.323, 0.035
ESR	–0.014	0.934	–0.041, 0.037	0.125	0.426	–0.017, 0.040	0.049	0.757	–0.053, 0.073
IL-1ß	–0.026	0.884	–0.008, 0.007	0.062	0.717	–0.004, 0.006	0.013	0.941	–0.011, 0.012
IL-6	0.134	0.505	–0.001, 0.002	0.233	0.227	0.000, 0.002	0.185	0.337	–0.001, 0.004
sIL-6R	–0.798	0.002	–0.009, –0.002	–0.945	< 0.001	–0.008, –0.003	–0.904	< 0.001	–0.017, –0.006
OPG	–0.563	0.032	–0.002, 0.000	–0.727	0.005	–0.002, 0.000	–0.666	0.009	–0.003, 0.000
RANKL	–0.117	0.518	–0.004, 0.002	–0.079	0.646	–0.003, 0.002	–0.105	0.543	–0.006, 0.003

BMI: body mass index; ESR: erythrocyte sedimentation rate; IL-1ß: interleukin 1ß: IL-6: interleukin 6; sIL-6R: soluble IL-6 receptor; OPG: osteoprotegerin; RANKL: receptor activator of nuclear factor-κB ligand.

absence of radiographic damage in patients with gout. These findings suggest that disturbances of crucial cytokines controlling bone homeostasis, OPG, and RANKL might be involved in the radiographic damage in gout, although consistent data were not established.

Infiltration of diverse inflammatory cells including monocytes and immature macrophages around tophi formed by MSU crystals are considered a hallmark in MSU-induced inflammation[1,2]. After exposure to MSU crystals, inflammatory cytokines secreted from infiltrating inflammatory cells, such as IL-1ß, IL-6, and sIL-6R, have been shown to be involved in initiation or amplification of acute inflammatory attacks of gout[6,7,8,9,10]. These cytokines have been demonstrated to be major regulator mediators of osteoclastogenesis or of increased bone-absorbing activity of osteoclasts[11,12]. Few data implicating these cytokines in osteoclast activation in gout have been described until now. Alwan, *et al* demonstrated, in a study using peritoneal mice macrophages, that enhanced bone resorption activity was induced from stimulation of MSU crystals and release of IL-1[16]. Bouchard, *et al* investigated alteration of the functional phenotype of human osteoblastic cells by stimulation of microcrystals, including MSU and calcium pyrophosphate dihydrate, in an analysis of bone destruction in crystal arthropathies[4]. That study demonstrated that microcrystals alone and with IL-1 significantly induced cyclooxygenase in osteoblastic cells, suggesting contributions of these functional changes to amplification of osteoblastic activity in bone destruction in microcrystal-induced arthropathies. These data suggest that IL-1 plays a role in the bone damage of gout. Our study showed higher

IL-1ß levels in patients with gout compared to those of healthy controls. However, serum IL-1ß levels were not related to scores of radiographic damage indices.

IL-6 is a pleiotropic cytokine with variable biological activities on target cells that, combined with sIL-6R, has been demonstrated to lead to activation of synovial cells and formation of osteoclasts, cells with a major effect in the bony erosion of rheumatoid arthritis (RA)[12]. Serum IL-6 levels in gout have been known to be higher than those in controls or patients with osteoarthritis (OA), while sIL-6R levels were not significantly different in controls and in other inflammatory arthritides[9,10]. Although we observed higher serum IL-6 levels in patients with gout than in the controls, serum IL-6 levels were not associated with radiographic damage scores. Serum IL-6 levels in gout also did not differ between the presence of and absence of radiographic damage. The IL-6/sIL-6R complex has a key role in the regulation of inflammation[17]. It is reported that sIL-6R in different rheumatic diseases was mainly released from hepatocytes and leukocytes[9]. At the acute inflammatory phase, activation of endothelial cells after local stimuli induces leukocyte recruitment. Sequentially, enhanced enrollment of neutrophils secretes the soluble form of IL-6R into the inflammatory site. And then, formation of the IL-6/sIL-6R complex (the transsignaling action of IL-6) contributes to the transition of neutrophils to monocyte recruitment. In our study, multivariate regression analysis showed that sIL-6R levels were inversely related to radiographic damage indices. In addition, serum sIL-6R levels in patients with radiographic damage were significantly lower than in patients without damage. This inverse relationship of serum sIL-6R levels to radiographic damage might be explained by the fact that enrolled study patients were in the chronic phase of gout without acute inflammation. Although IL-6 persistently works irrespective of the acute or chronic inflammation status, the transsignaling action of the IL-6/sIL-6R complex might be mainly involved in the acute or resolving phase of inflammation[17]. Monocytes rather than neutrophils are crucial cells in the chronic phase and are related to lack of secretion of sIL-6R. Therefore, the pathogenic role of sIL-6R in gout could be reduced in the chronic phase of radiographic damage. Because the pathogenic roles of IL-6 and/or sIL-6R in the bone erosion of gouty arthritis are still undefined, study of the role of these cytokines is necessary.

It has been established that persistent hyperuricemia could contribute to the development of tophi in patients with gout. The use of urate-lowering agents such as benzbromarone or allopurinol significantly reduces the size of tophi[18]. There has been little clinically relevant interaction between uric acid and RANKL demonstrated in osteoclast activation. MSU crystals have not been shown to directly influence the formation of osteoclast-like cells[5]. However, a conditioned medium from murine ST2 cells treated with MSU crystals in the presence of RANKL significantly induced osteoclast formation, compared to the same procedure in the absence of MSU crystal stimulation. These data indicated that MSU crystals and RANKL could be mutually cooperative in generating radiographic bone damage in gout. However, our study did not demonstrate significant correlation between serum uric acid level and RANKL level in gout.

Traditional risk factors for differentiating gout from asymptomatic hyperuricemia have been illustrated and include age, obesity, alcohol consumption, use of diuretics, and high serum uric acid level[19,20,21]. However, risk factors for radiographic damage in established gout have not been characterized. From previous data, the presence of intraosseous tophi at affected joints might be considered the strongest indicator for radiographic bone damage[5,22,23]. Our study identified significant association scores of radiographic damage indices with age, ESR, and BMI in simple correlation analysis. ESR level has reflected disease severity well, paralleling the number of involved joints and gouty dactylitis in gouty arthritis[24,25]. It can be assumed that ESR might be an indicator of radiographic severity in gout. Interestingly, patients with higher BMI showed lower radiographic joint narrowing scores in our study. Obesity generally predisposes patients to more severe forms of some musculoskeletal diseases, including OA. However, high BMI has been shown to have a protective effect on joint or bone damage, such as in osteoporosis and RA[26]. A recent RA cohort study assessing the association between BMI and radiological joint damage paradoxically showed that higher BMI was associated with less severe radiographic change 1 year after diagnosis[26]. In our study, age, ESR, and BMI were not considered risk factors for radiographic bone damage after adjustment for confounding factors.

Our study showed that the inflammatory cytokines sIL-6R and OPG were negatively associated with radiographic bone damage in gout. However, our study did not show significant relationships between radiographic bone damage and other inflammatory cytokines including IL-1ß, IL-6, and RANKL. The roles for potent cytokines in bone damage from gout should be examined in larger study populations.

REFERENCES

1. Terkeltaub RA. Clinical practice. Gout. N Engl J Med 2003;349:1647-55.
2. Bieber JD, Terkeltaub RA. Gout: on the brink of novel therapeutic options for an ancient disease. Arthritis Rheum 2004;50:2400-14.
3. Perez-Ruiz F, Dalbeth N, Urresola A, de Miguel E, Schlesinger N. Imaging of gout: findings and utility. Arthritis Res Ther 2009;11:232.
4. Bouchard L, de Médicis R, Lussier A, Naccache PH, Poubelle PE. Inflammatory microcrystals alter the functional phenotype of human osteoblast-like cells in vitro: synergism with IL-1 to overexpress cyclooxygenase-2. J Immunol 2002;168:5310-7.
5. Dalbeth N, Smith T, Nicolson B, Clark B, Callon K, Naot D, et al. Enhanced osteoclastogenesis in patients with tophaceous gout: urate crystals promote osteoclast development through interactions with stromal cells. Arthritis Rheum 2008;58:1854-65.
6. Di Giovine FS, Malawista SE, Nuki G, Duff GW. Interleukin 1 (IL 1) as a mediator of crystal arthritis. Stimulation of T cell and

synovial fibroblast mitogenesis by urate crystal-induced IL 1. J Immunol 1987;138:3213-18.
7. Chen CJ, Shi Y, Hearn A, Fitzgerald K, Golenbock D, Reed G, et al. MyD88-dependent IL-1 receptor signaling is essential for gouty inflammation stimulated by monosodium urate crystals. J Clin Invest 2006;116:2262-71.
8. Giamarellos-Bourboulis EJ, Mouktaroudi M, Bodar E, van der Ven J, Kullberg BJ, Netea MG, et al. Crystals of monosodium urate monohydrate enhance lipopolysaccharide-induced release of interleukin 1 beta by mononuclear cells through a caspase 1-mediated process. Ann Rheum Dis 2009;68:273-8.
9. Desgeorges A, Gabay C, Silacci P, Novick D, Roux-Lombard P, Grau G, et al. Concentrations and origins of soluble interleukin 6 receptor-alpha in serum and synovial fluid. J Rheumatol 1997;24:1510-6.
10. Tsai PC, Chen CJ, Lai HM, Chang SJ. Analysis of polymorphisms in the promoter region and protein levels of interleukin-6 gene among gout patients. Clin Exp Rheumatol 2008;26:841-7.
11. Jimi E, Nakamura I, Duong LT, Ikebe T, Takahashi N, Rodan GA, et al. Interleukin 1 induces multinucleation and bone-resorbing activity of osteoclasts in the absence of osteoblasts/stromal cells. Exp Cell Res 1999;247:84-93.
12. Tamura T, Udagawa N, Takahashi N, Miyaura C, Tanaka S, Yamada Y, et al. Soluble interleukin-6 receptor triggers osteoclast formation by interleukin 6. Proc Natl Acad Sci USA 1993;90:11924-8.
13. Wallace SL, Robinson H, Masi AT, Decker JL, McCarty DJ, Yü TF. Preliminary criteria for the classification of the acute arthritis of primary gout. Arthritis Rheum 1977;20:895-900.
14. Dalbeth N, Clark B, McQueen F, Doyle A, Taylor W. Validation of a radiographic damage index in chronic gout. Arthritis Rheum 2007;57:1067-73.
15. Nguyen C, Ea H-K, Palazzo E, Lioté F. Tophaceous gout: an unusual cause of multiple fractures. Scand J Rheumatol 2010;39:93-6.
16. Alwan WH, Dieppe PA, Elson CJ, Bradfield JW. Hydroxyapatite and urate crystal induced cytokine release by macrophages. Ann Rheum Dis 1989;48:476-82.
17. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther 2006;8 Suppl 2:S3.
18. Perez-Ruiz F, Calabozo M, Pijoan JI, Herrero-Beites AM, Ruibal A. Effect of urate-lowering therapy on the velocity of size reduction of tophi in chronic gout. Arthritis Rheum 2002;47:356-60.
19. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-6.
20. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifications for gout. Arthritis Res Ther 2006;8 Suppl 1:S2.
21. Lin KC, Lin HY, Chou P. The interaction between uric acid level and other risk factors on the development of gout among asymptomatic hyperuricemic men in a prospective study. J Rheumatol 2000;27:1501-5.
22. Bloch C, Hermann G, Yu TF. A radiologic reevaluation of gout: a study of 2,000 patients. AJR Am J Roentgenol 1980;134:781-7.
23. Dalbeth N, Clark B, Gregory K, Gamble G, Sheehan T, Doyle A, et al. Mechanisms of bone erosion in gout: a quantitative analysis using plain radiography and computed tomography. Ann Rheum Dis 2009;68:1290-5.
24. Roseff R, Wohlgethan JR, Sipe JD, Canoso JJ. The acute phase response in gout. J Rheumatol 1987;14:974-7.
25. Andracco R, Zampogna G, Parodi M, Cimmino MA. Risk factors for gouty dactylitis. Clin Exp Rheumatol 2009;27:993-5.
26. van der Helm-van Mil AH, van der Kooij SM, Allaart CF, Toes RE, Huizinga TW. A high body mass index has a protective effect on the amount of joint destruction in small joints in early rheumatoid arthritis. Ann Rheum Dis 2008;67:769-74.