Low Body Mass Index Is Adversely Associated with Radiographic Joint Damage in Indian Patients with Early Rheumatoid Arthritis

UMA D. VELPULA, SUMEET AGRAWAL, JOE THOMAS, V.N. NAGA PRABU, LIZA RAJASEKHAR, and GUMDAL NARSIMULU

ABSTRACT. ***Objective.*** Various factors affect joint damage in rheumatoid arthritis (RA). The influence of body mass index (BMI) is not adequately known. As BMI is potentially modifiable, we studied its influence on radiological joint damage in patients with RA.

Methods. Treatment-naive patients with early RA (< 24 mo) were included. Demographic data were collected along with swollen joint count (SJC), tender joint count (TJC), erythrocyte sedimentation rate (ESR), and IgM-rheumatoid factor (IgM-RF). Radiographs of hands and feet were obtained. BMI and Disease Activity Score for 28-joint count (DAS28-ESR) were calculated. Joint damage was assessed using the Simplified Erosions Narrowing Score (SENS).

Results. A total of 101 patients were studied (81 women; mean age 41.91 ± 11.99 yrs). Mean disease duration was 10.77 ± 6.73 months; 55 patients (54.5%) were IgM-RF-positive. Mean BMI was 22.82 ± 4.66 kg/m^2 with 24 (23.8%) patients having low, 42 (41.6%) normal, and 35 (34.7%) high BMI. Mean SENS score was 16.81 ± 11.10; mean DAS28 was 6.23 ± 0.96. Significant correlation was noted between SENS and DAS28 ($r = 0.28$; $p < 0.005$). There was significant negative correlation between BMI and SENS ($r = –0.509$; $p < 0.0005$). In patients with low BMI, mean SENS (26.62 ± 13.45) was significantly higher than in patients with normal (15.88 ± 8.38; $p < 0.001$) and high BMI (11.20 ± 7.32; $p < 0.001$). Patients with normal BMI also had significantly higher SENS scores than those with high BMI ($p < 0.05$). One-way ANOVA did not reveal significant differences in DAS28 between groups. SENS was significantly higher in the IgM-RF-positive group (19.55 ± 11.36) than in the IgM-RF-negative group (13.54 ± 9.94; $p < 0.01$); DAS28 was not different between the 2 groups (6.22 ± 0.98 vs 6.26 ± 0.96, respectively). Within the 2 IgM-RF groups, a significant negative correlation was seen between BMI and SENS. Multiple regression analysis revealed RF, DAS28, and BMI were independently associated with SENS. BMI accounted for 23.04% of the variance in SENS independent of DAS28 and IgM-RF.

Conclusion. Low BMI is adversely associated with joint damage in patients with early RA. (First Release Nov 15 2010; J Rheumatol 2011;38:434–8; doi:10.3899/jrheum.100535)

Key Indexing Terms:
BODY MASS INDEX DISEASE ACTIVITY SCORE RHEUMATOID ARTHRITIS
OBESITY RADIOLOGICAL DAMAGE SIMPLIFIED EROSION NARROWING SCORE

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease affecting about 1% of the adult population. The hallmark of this disease is synovial inflammation and its potential to cause cartilage and bone damage, with consequent effects on joint integrity. The mechanisms leading to this destruction remain unclear. Proinflammatory cytokines and activation of osteoclasts appear to have a crucial role[1,2,3]. The destructive consequences of the disease are evident by the appearance of erosions in 10%–26% of patients within 3 months of disease onset, in over 60% within one year, and in about 75% of patients within 2 years[4,5]. More recently, RA inflammation has also emerged as an important cause of cardiovascular morbidity and mortality.

The joint damage does not progress predictably in every patient. There are significant interpatient differences in the rate at which the joint damage progresses; various factors associated with it have been studied over years. Unfortunately, most of these factors are nonmodifiable. One that seems to be of clinical significance but has not been adequately studied is the body mass index (BMI), which reflects the nutritional status of an individual. In a general population, high BMI has been associated with increased risk of conditions such as diabetes mellitus, cardiovascular disease, stroke, and osteoarthritis. Interestingly, a few recent studies have paradoxically shown a protective effect of

From the Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, India.

U.D. Velpula, DNB, Resident; S. Agrawal, DM, Assistant Professor; J. Thomas, MD, Resident; V.N.N. Prabu, MD, Resident; L. Rajasekhar, MD, Associate Professor; G. Narsimulu, MD, Professor.

Address correspondence to Dr. S. Agrawal, Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, India.
E-mail: sumeet.drsumeetagrawal@gmail.com

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higher BMI on cardiovascular disease in patients with RA[6,7]. A few studies have also shown low BMI to be associated with increased radiographic joint damage in patients with RA[8,9,10]. It is an important clinical variable because of the potential to be favorably modified to influence outcomes in patients with RA.

It is known that factors influencing disease processes may not be uniformly applicable across ethnic groups. Indians represent a race with a population distribution of body fat and BMI very different from those of Caucasians[11,12]. Whether low BMI protects against joint damage in Indian patients with RA is not known. We investigated this concept hoping to establish its generalizability.

MATERIALS AND METHODS

This study was conducted in the outpatient clinic of the Department of Rheumatology, Nizam's Institute of Medical Sciences, Hyderabad, India. The study was approved by the institutional ethics committee. Informed consent was obtained from all participating patients. Treatment-naive patients with early RA (< 24 months) fulfilling American College of Rheumatology criteria[13] were included. Smoking and alcohol abuse at incidence and thereafter were exclusion criteria.

Data were collected on age, sex, height, weight, swollen joint count, tender joint count, erythrocyte sedimentation rate (ESR; Westergren method), and IgM rheumatoid factor (IgM-RF). Radiographs were taken of both hands with wrists (posteroanterior views) and both feet (anteroposterior views). BMI (weight in kg/height in m^2) and Disease Activity Score-28 (DAS28 ESR) were calculated in all subjects. Based upon the BMI values, patients were assigned to low, normal, or high BMI groups following the classification criteria of the World Health Organization[14].

Radiographic joint damage was assessed using the Simplified Erosions Narrowing Score (SENS) as this was considered more feasible[15,16,17]. In SENS, joint erosions are scored in 32 joints in both hands and wrists [10 metacarpophalangeal (MCP) joints, 8 proximal interphalangeal (PIP) joints, 2 interphalangeal joints of the thumbs, right and left first metacarpal bone, right and left radius and ulnar bones, right and left trapezium and trapezoid (as one unit; multiangular), right and left scaphoid bones, right and left lunate bones] and 12 joints in both feet [10 metatarsophalangeal (MTP) joints and 2 interphalangeal joints of the big toes]. Joint space narrowing (JSN) is assessed in 30 joints in both hands and wrists [10 MCP joints, 8 PIP joints, right and left third, fourth, fifth carpometacarpal joints, right and left multangular-scaphoid joints, right and left capitate-scaphoid-lunate joints, right and left radiocarpal joints] and 12 joints in both feet (10 MTP joints and 2 interphalangeal joint of the big toes). A joint is scored as affected "1" if it displays any erosion and as affected "1" for JSN. The score for each joint can therefore range from 0 to 2. The maximum total score of SENS per patient is 86.

Statistical analysis was done using SPSS statistical software, version 15.

RESULTS

A total of 101 patients were studied; 81 (80.2%) women and 20 (19.8%) men. The mean age was 41.91 ± 11.99 years (range 19–72 yrs). Mean duration of disease was 10.77 ± 6.73 months (range 3–24 mo). Fifty-five (54.5%) patients were IgM-RF-positive (> 40 U/l). The mean BMI was 22.82 ± 4.66 kg/m^2, with 24 (23.8%) patients having low BMI (< 18.5), 42 (41.6%) having normal BMI (18.5–24.9), and 35 (34.7%) having high BMI (> 25). The mean SENS score was 16.81 ± 11.10 (range 3–54); the mean DAS28 was 6.23 ± 0.96. There was a significant correlation between SENS and DAS28 ($r = 0.28$, $p < 0.005$). Patients' characteristics have been summarized in Table 1.

The relationship between BMI and SENS was investigated using Pearson correlation coefficients. There was a strong negative correlation between the 2 variables ($r = –0.509$, $p < 0.0005$; Figure 1). Also, in patients with low BMI, mean SENS (26.62 ± 13.45) was significantly higher than in those with normal BMI (15.88 ± 8.38) ($p < 0.001$) and high BMI (11.20 ± 7.32) ($p < 0.001$). Similarly, patients in the normal BMI group also had significantly higher SENS than those in the high BMI group ($p < 0.05$). However, there was no correlation between SENS and DAS28 in any of the groups. One-way ANOVA did not reveal significant differences in DAS28 between groups. Post-hoc analysis for multiple comparisons also did not show significant differences in DAS28 between any 2 of the groups. Since our study cohort had a higher proportion of female patients as compared to other reported RA cohorts, in order to exclude the likelihood of this exerting bias on the overall results, we also analyzed the correlation between BMI and SENS in male and female groups separately. There was significant negative correlation between them in both these groups as well (female group, $r = –0.449$, $p < 0.0005$; male group, $r = –0.678$, $p < 0.001$).

Comparing the IgM-RF-positive and IgM-RF-negative groups, the SENS was significantly higher in the IgM-RF-positive group than in the IgM-RF-negative group; however, the DAS28 was not different in the 2 groups, nor was the BMI (Table 2). Within the IgM-RF-positive and IgM-RF-negative patient groups as well, a significant negative correlation was seen between BMI and SENS (IgM-RF-positive group, $r = –0.55$, $p < 0.0001$; IgM-RF-negative group, $r = –0.36$, $p < 0.05$).

Multiple regression analysis was further used to investigate the unique contributions of IgM-RF, DAS28, and BMI (as independent variables) to SENS (dependent variable). The result of the multiple regression model ($R^2 = 0.345$, $p < 0.0005$) is summarized in Table 3 and indicates that IgM-RF, DAS28, and BMI were independently associated with SENS. Independent of DAS28 and IgM-RF, BMI accounted for 23.04% of the variance in SENS according to this model.

DISCUSSION

Our study shows that BMI significantly influences joint damage in patients with early RA, patients with high BMI having less joint damage than patients with normal or low BMI. These findings are supported by other studies that also show that high BMI protects against joint damage in patients with RA[8,9,10].

One of our striking findings was that a considerable proportion of patients (about a quarter) had low BMI. In contrast, Westhoff, *et al* reported only 6/767 (0.78%) of their patients having a low BMI[10]. This might be a reflection of

Table 1. Characteristics of patients.

Characteristics	Total, n = 101	Low BMI, n = 24	Normal BMI, n = 42	High BMI, n = 35	p, ANOVA*
Women, n (%)	81 (80.2)	18 (75)	30 (71.4)	33 (93.4)	NS†
Age, yrs, mean ± SD	41.9 ± 11.9	39.88 ± 13.02	42.95 ± 12.13	42.06 ± 11.23	NS
RA disease duration, mo, mean ± SD	10.77 ± 6.73	13.5 ± 7.6	9.3 ± 5.8	10.6 ± 6.7	NS
IgM-RF-positive, n (%)	55 (54.5)	15 (62.5)	22 (52.4)	18 (51.4)	NS†
RF, IU/ml	54.44 ± 42.74	57.08 ± 46.67	53.14 ± 39.30	54.17 ± 45.06	NS
BMI, kg/m^2	22.82 ± 4.66	16.69 ± 1.16	21.94 ± 1.94	27.90 ± 2.39	NA
SENS, mean ± SD	16.8 ± 11.1	26.62 ± 13.45	16.05 ± 8.34	11.27 ± 7.40	< 0.0005
DAS28, mean ± SD	6.2 ± 0.9	6.62 ± 0.87	6.04 ± 0.93	6.21 ± 1.01	NS

RF: rheumatoid factor; BMI: body mass index; SENS: Simplified Erosion Narrowing Score; DAS28: Disease Activity Score 28-joint count; NS: nonsignificant; NA: not applicable. * Between low, normal, and high BMI groups. † Kruskal-Wallis test.

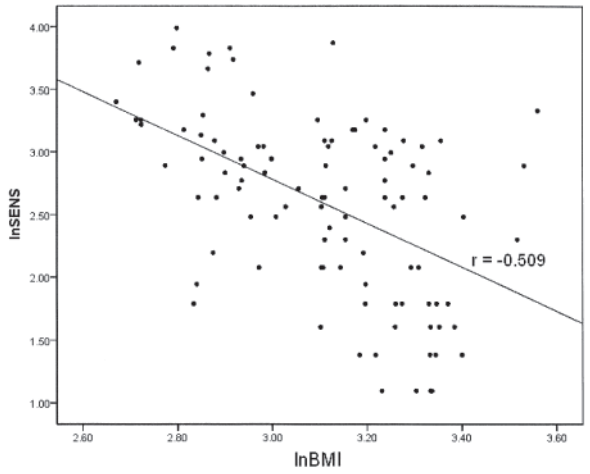

Figure 1. Scatterplot showing negative correlation of natural logarithm (ln) transformation of the Simplified Erosions Narrowing Score (SENS) and body mass index (BMI).

Table 2. Comparison of IgM-RF-positive and negative groups.

	IgM-RF-positive	IgM-RF-negative	p
SENS	19.55 ± 11.36	13.54 ± 9.94	< 0.01
DAS28	6.22 ± 0.98	6.26 ± 0.96	NS
BMI	23.08 ± 0.64	22.60 ± 0.66	NS

SENS: Simplified Erosion Narrowing Score; DAS28: Disease Activity Score 28-joint count; BMI: Body Mass Index; RF: rheumatoid factor; NS: not significant.

the nutritional status of the population from which the study cohort is derived. It is unlikely to be due to high inflammatory state, as the disease activity was comparable in the low, normal, and high BMI groups. Moreover, a recent study has shown that inflammation does not seem to influence BMI in RA[18]. This finding is possibly of considerable significance. Since high BMI is found to protect against radiographic damage, it raises an important question — does poor nutritional state (and hence low BMI) in a population predispose RA patients from that community to accrue higher damage?

Our findings of a graded decrease in radiological score from low through normal to high BMI groups in the presence of comparable disease activity supports the concept proposed by Kauffman, *et al* of BMI being an "inflammation-independent" factor determining joint damage, which has also been endorsed by the results from Westhoff, *et al*[8,10].

RF positivity is well known to be associated with higher damage[19,20]. The same is also evident here. We also found higher BMI to be protective in both RF-positive and negative groups. Although Westhoff, *et al*[10] did not find BMI to protect against joint damage in an RF-negative group, they have suggested that due to the overall lower joint destruction in the RF-negative patients, the potential association between BMI and joint damage could not be seen in their study. Our results reinforce their suggestion and prove that BMI protects even in an RF-negative group. The lower joint destruction in RF-negative patients might also be the explanation of why the strength of association was weaker in the RF-negative group compared to that in the RF-positive group in our study.

The mechanisms by which high BMI protects against joint damage are not entirely known. One possible link that has been studied is white adipose tissue, which is known to be an active producer of adipokines that play an important role in inflammation and immunity[21]. Adiponectin is strongly associated with radiographic damage and independently accounts for about 6% of the variability in radiographic scores, which was comparable to RF[22]. To date no correlation of adiponectin levels and disease activity have been found to support the "inflammation-independent" effects of BMI[23]. Adiponectin also has various antiinflammatory effects, such as induction of interleukin 10 (IL-10) and IL-1 receptor antagonist production by monocytes-macrophages, inhibition of IL-6 and tumor necrosis factor-α, and other mechanisms[24,25,26,27,28]. Adiponectin concentrations in plasma of RA patients were found to be higher than in con-

Table 3. Multiple regression analysis with Simplified Erosion Narrowing Score as dependent variable.

Variables	Coefficients Beta	p	95% CI	Part Correlation
IgM-RF	0.236	0.006	0.018 to 0.104	0.276
BMI	–0.448	< 0.0005	–1.455 to –0.677	–0.483
DAS28	0.299	0.001	1.531 to 5.329	0.342

DAS28: Disease Activity Score 28-joint count; BMI: body mass index; RF: rheumatoid factor.

trols[29,30,31]. It has been suggested that high adiponectin levels of patients with RA represent an attempt to overcome the proinflammatory state[32]. Unlike adiponectin, leptin is of a more proinflammatory nature; however, its role in the pathogenesis of RA is controversial[32,33,34].

Another suggested mechanistic link between BMI and joint damage in obese patients is through the increased bioavailability of estrogen, which has antiinflammatory effects and has a positive influence on bone turnover[35]. BMI itself is influenced by multiple other factors such as genetic, lifestyle, and comorbid conditions. Therefore, the possibilities of shared genetic components, environmental and dietary factors, and comorbid conditions influencing the effects of BMI on joint damage need to be examined.

Our results further reinforce that BMI as an independent variable is significantly associated with joint damage in patients with RA and that this remains a factor across ethnicities. It also raises the issue of whether the nutritional status of the population has any bearing upon the extent of joint damage in patients with RA from that population. This can only be addressed by large population-based studies. With more data supporting the effect of BMI on RA, it is time now to incorporate it as a potentially modifiable variable for RA outcomes.

The limitations of our study include its cross-sectional design. A relatively low proportion of RF positives and higher proportion of females compared to other RA cohorts also might limit the generalizability of the results. Moreover, same BMI does not correspond to the same degree of fat content in different populations and so may not be the most appropriate measure to compare the fat content. This may have a bearing on the influence of BMI on joint damage.

REFERENCES

1. Redlich K, Hayer S, Maier A, Dunstan CR, Tohidast-Akrad M, Lang S, et al. Tumor necrosis factor-α mediated joint destruction is inhibited by targeting osteoclasts with osteoprotegerin. Arthritis Rheum 2002;46:785-9.
2. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 1996;14:397-440.
3. Gravellese EM, Harada Y, Wang JT, Gorn AH, Thornhill TS, Goldring SR. Identification of cell types responsible for bone resorption in rheumatoid arthritis and juvenile rheumatoid arthritis. Am J Pathol 1998;152:943-51.
4. Machold KP, Stamm TA, Eberl GJM, Nell VKP, Dunky A, Uffmann M, et al. Very recent onset arthritis — clinical, laboratory and radiological findings during the first year of disease. J Rheumatol 2002;29:2278-87.
5. Harrison B, Symmons D. Early inflammatory polyarthritis: results from the Norfolk Arthritis Register with a review of the literature. II. Outcome at three years. Rheumatology 2000;39:939-49.
6. Escalante A, Haas RW, del Rincon I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Arch Intern Med 2005;165:1624-9.
7. Kremers HM, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Prognostic importance of low body mass index in relation to cardiovascular mortality in rheumatoid arthritis. Arthritis Rheum 2004;50:3450-7.
8. Kaufmann J, Kielstein V, Kilian S, Stein G, Hein G. Relation between body mass index and radiological progression in patients with rheumatoid arthritis. J Rheumatol 2003;30:2350-5.
9. 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.
10. Westhoff G, Rau R, Zink A. Radiographic joint damage in early rheumatoid arthritis is highly dependent on body mass index. Arthritis Rheum 2007;56;3575-82.
11. Wulan SN, Westerterp KR, Plasqui G. Ethnic differences in body composition and the associated metabolic profile: a comparative study between Asians and Caucasians. Maturitas 2010;65:315-9.
12. Deurenberg P, Deurenberg-Yap M, Guricci S. Asians are different from Caucasians and from each other in their body mass index/body fat per cent relationship. Obes Rev 2002;3:141-6.
13. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
14. World Health Organization expert consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157-63.
15. van der Heijde D, Dankert T, Nieman F, Rau R, Boers M. Reliability and sensitivity to change of a simplification of the Sharp/van der Heijde radiological assessment in rheumatoid arthritis. Rheumatology 1999;38;941-7.
16. Boini S, Guillemin F. Radiographic scoring methods as outcome measures in rheumatoid arthritis: properties and advantages. Ann Rheum Dis 2001;60:817-27.
17. Dias EM, Lukas C, Landewé R, Fatenejad S, van der Heijde D. Reliability and sensitivity to change of the Simple Erosion Narrowing Score compared with the Sharp-van der Heijde method for scoring radiographs in rheumatoid arthritis. Ann Rheum Dis 2008;67:375-9.
18. Stavropoulos-Kalinoglou A, Metsios GS, Smith JP, Panoulas VF, Douglas KM, Jamurtas AZ, et al. What predicts obesity in patients with rheumatoid arthritis? An investigation of the interactions between lifestyle and inflammation. Int J Obes 2010;34:295-301.
19. Nell VP, Machold KP, Stamm TA, Eberl G, Heinzl H, Uffmann M, et al. Autoantibody profiling as early diagnostic and prognostic tool for rheumatoid arthritis. Ann Rheum Dis 2005;64:1731-6.
20. Bas S, Genevay S, Meyer O, Gabay C. Anti-cyclic citrullinated peptide antibodies, IgM and IgA rheumatoid factors in the diagnosis and prognosis of rheumatoid arthritis. Rheumatology 2003; 42:677-80.
21. Fantuzzi G. Adipose tissue, adipokines, inflammation. J Allergy Clin Immunol 2005;115:911-9.
22. Giles JT, Allison M, Bingham CO 3rd, Scott WM Jr, Bathon JM. Adiponectin is a mediator of the inverse association of adiposity

with radiographic damage in rheumatoid arthritis. Arthritis Rheum 2009;61:1248-56.
23. Laurberg TB, Frystyk J, Ellingsen T, Hansen IT, Jørgensen A, Tarp U, et al. Plasma adiponectin in patients with active, early, and chronic rheumatoid arthritis who are steroid- and disease-modifying antirheumatic drug-naive compared with patients with osteoarthritis and controls. J Rheumatol 2009;36:1885-91.
24. Masaki T, Chiba S, Tatsukawa H, Yasuda T, Noguchi H, Seike M, et al. Adiponectin protects LPS-induced liver injury through modulation of TNF-α in KK-Ay mice. Hepatology 2004;40:177-84.
25. Wolf AM, Wolf D, Rumpold H, Enrich B, Tilg H. Adiponectin induces the anti-inflammatory cytokines IL-10 and IL-1 RA in human leukocytes. Biochem Biophys Res Commun 2004; 323:630-5.
26. Wulster-Radcliffe MC, Ajuwon KM, Wang J, Christian JA, Spurlock ME. Adiponectin differentially regulates cytokines in porcine macrophages. Biochem Biophys Res Commun 2004;316:924-9.
27. Senolt L, Pavelka K, Housa D, Haluzík M. Increased adiponectin is negatively linked to the local inflammatory process in patients with rheumatoid arthritis. Cytokine 2006;35:247-52.
28. Lago F, Dieguez C, Gómez-Reino J, Gualillo O. Adipokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716-24.
29. Rho YH, Solus J, Sokka T, Oeser A, Chung CP, Gebretsadik T, et al. Adipocytokines are associated with radiographic joint damage in rheumatoid arthritis. Arthritis Rheum 2009;60:1906-14.
30. Ebina K, Fukuhara A, Ando W, Hirao M, Koga T, Oshima K, et al. Serum adiponectin concentrations correlate with severity of rheumatoid arthritis evaluated by extent of joint destruction. Clin Rheumatol 2009;28:445-51.
31. Schäffler A, Ehling A, Neumann E, Herfarth H, Tarner I, Schölmerich J, et al. Adipocytokines in synovial fluid. JAMA 2003;290:1709-10.
32. Otero M, Lago R, Lago F, Casanueva FF, Dieguez C, Gómez-Reino JJ, et al. Leptin from fat to inflammation: Old questions and new insights. FEBS Lett 2005;579:295-301.
33. Stofkova A. Leptin and adiponectin: from energy and metabolic dysbalance to inflammation and autoimmunity. Endocr Regul 2009;43:157-68.
34. Lago F, Dieguez C, Gomez-Reino J, Gualillo O. Adokines as emerging mediators of immune response and inflammation. Nat Clin Pract Rheumatol 2007;3:716-24.
35. Carlsten H. Immune responses and bone loss: the estrogen connection. Immunol Rev 2005;208:194-206.