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Neutrophil-lymphocyte ratio may be superior to C-reactive protein for predicting the occurrence of postmenopausal osteoporosis

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Objective: Recent studies revealed that inflammation plays a critical role in bone remodeling and the pathogenesis of postmenopausal osteoporosis, a major health concern. Neutrophil-lymphocyte ratio (NLR) is a cost-effective marker of inflammation that has been linked with several diseases. This study aimed to compare NLR and C-reactive protein (CRP) levels in osteopenic, osteoporotic, and control subjects and to assess the correlation between NLR levels, CRP, and bone mineral density (BMD) in postmenopausal women.

Methods: In this cross-sectional study, the relationship between NLR, CRP, and BMD in 438 women was investigated using uni- and multivariate analyses. BMD (g/cm^2) was measured by dual-energy X-ray absorptiometry (DEXA) at the lumbar spine and femur. Complete blood count (CBC), CRP, glucose/lipid metabolism, and established risk factors were determined.

Results: In the osteoporotic group, NLR and CRP levels were found to be elevated as compared to the osteopenic and control groups (NLR: 4.68 ± 0.72, 3.17 ± 0.43, 2.01 ± 0.54; CRP: 12.3 ± 4.1, 4.1 ± 2.7, 3.2 ± 2.1, respectively). A negative correlation was present between NLR and the lumbar spine (L2-L4) and femoral neck BMD after adjusting other risk factors. There was no correlation between CRP levels and BMD after adjusting other risk factors. NLR was significantly associated with L2-L4 BMD (ß = -0.653, p<0.001) and femoral neck BMD (ß = -0.178, p<0.001), but CRP level had no association with BMD in a multivariate model.

Conclusions: Our data indicate that NLR may be a better predictor than CRP for occurrence of osteoporosis in postmenopausal women.

Key words: NLR, inflammation, CRP, osteoporosis, BMD, menopause

Osteoporosis has become a major public health problem, affecting about 200 million people worldwide, including one third of all postmenopausal women (National Osteoporosis Foundation 2008). Osteoporosis has been defined as a skeletal disease characterized by compromised bone strength predisposing a person to an increased risk of fracture (National Osteoporosis Foundation 2008). This places an immense burden on healthcare systems, due to the 1.5 million osteoporosis-related fractures each year, which often lead to hospitalizations, emergency room and physician visits, and nursing home placements. Eighty percent of individuals with osteoporosis are women, largely due to the marked loss in bone density associated with estrogen deficiency that accompanies loss of ovarian function at menopause (National Osteoporosis Foundation 2008). Several inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus,

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inflammatory bowel disease, celiac disease, cystic fibrosis, and chronic obstructive pulmonary disease have been associated with bone resorption. The link between osteoclast, macrophage colony stimulating factor, and pro-inflammatory cytokines explains the association between inflammation and osteoporosis. Some studies showed that pro-inflammatory cytokines are capable of stimulating osteoclastic bone resorption, including interleukin (IL)-1 (Kimble et al. 1995), tumor necrosis factor alpha (TNF-α) (Names 2003), IL-6 (Jilka et al. 1992), IL-11 (Girasole et al. 1994), and IL-15 (Ogata et al. 1999). Moreover, a recent study demonstrated that elevated levels of inflammatory markers were associated with an increased risk of hip fractures in older women (Lacativa and Farias 2010; Barbour et al. 2012).

Neutrophil-lymphocyte ratio (NLR) is a simple, inexpensive and useful index of systemic inflammatory burden that correlates with prognosis in distinct disease states (Bhat et al. 2013). It has been generally investigated in sepsis (Terradas et al. 2012), cardiovascular (Bhat et al. 2013) and neoplastic diseases (Guthrie et al. 2013). Inflammatory conditions are due to activity of osteoclasts (Chakravarti et al. 2009). Lipopolysaccharide (LPS) promotes the expression of membrane NF-κB ligand (RANKL) in human blood neutrophils (Chakravarti et al. 2009; Kikuta et al. 2013). RANKL-mediated signaling pathway plays essential roles in the regulation of osteoclastogenesis and activation of osteoclastic bone resorption (Kikuta et al. 2013). NLR may reflect activated neutrophils and relative lymphopenia. Activated neutrophils expressed RANKL and may promote the osteoclastic bone resorption.

C-reactive protein (CRP) is a marker of general systemic inflammation and prototype of acute-phase protein (Ansar and Ghosh 2013). CRP is a member of pentraxin family which is secreted by the liver in response to a variety of inflammatory cytokines (Ansar and Ghosh 2013). The relationship between CRP and many diseases such as cardiovascular disease, atherosclerosis, diabetes, cancer was investigated (Ansar and Ghosh 2013). CRP associated with bone mineral density in a population study (de Pablo et al. 2012) and CRP is an independent risk factor for all fractures in women (Pasco et al. 2006) and men (Eriksson et al. 2013).

We aimed to evaluate alterations in NLR levels in postmenopausal osteoporosis patients and the correlation of NLR levels with clinical and other laboratory parameters. In addition, we compare NLR and CRP levels to their predictive ability for postmenopausal osteoporosis occurrence.

Materials and Methods

Study population. A total of 438 females who were referred to the outpatient clinic were included between January 2008 and December 2011 in this cross-sectional study. Informed consent was obtained from every subject. Investigations were in accordance with the Declaration of Helsinki. Approval for this study was granted by Turgut Ozal University local ethical committee (B302FTH0200000/6).

Clinical characteristics. All the subjects underwent physical examination, including anthropometric and blood pressure measurements. Blood pressure was determined using a mercury-gravity sphygmomanometer in a sitting position after a 15 min rest. All patients were questioned for prescribed medication history and history of comorbidities, especially diabetes mellitus (DM), and coronary artery disease (CAD). Body mass index (BMI) was calculated as weight divided by squared height (kg/m^2). Control subjects were individuals with normal BMD levels who were referred to the hospital for routine checkups.

Biochemical parameters. After a 12 h overnight fast, blood samples were collected from participants. Laboratory tests were conducted, including complete blood count (CBC), fasting plasma glucose (FPG), erythrocyte sedimentation rate (ESR), CRP, sodium (Na), potassium (K), blood urine nitrogen (BUN), creatinine, calcium (Ca), total protein, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), plasma levels of total cholesterol (TC), low-density lipoprotein (LDL-C) and high-density lipoprotein (HDL-C) cholesterol, triglyceride (TG), thyroid stimulating hormone (TSH), and vitamin D by a hospital autoanalyzer. All CBC analysis was performed in the hematology laboratory of our hospital. CBC analysis was performed with the same analyzer within 1 h of collection of blood samples with the use of a Coulter Gen-S Hematology Analyzer (Beckman Coulter Corp, Hialeah, Florida).

Bone mineral density (BMD) measurement. BMD was measured using a Hologic QDR 4500A dual-energy X-ray absorptiometer (Bedford, MA, USA) at the lumbar spine (L2–L4) and femoral neck. The T-score was determined from the BMD, which was calculated as the bone mineral content divided by the area (g/cm^2). The T-score corresponds to the number of standard

deviations from the mean of a gender-matched reference population of young adults, as provided by the manufacturer. Osteopenia or osteoporosis was defined according to lowest measured T-score value in either the spine or the femoral neck. Diagnostic classification was based on the World Health Organization criteria: a BMD T-score ≥ -1.0 is normal; from -1.0 to -2.5 is indicative of low bone mass (osteopenia); and ≤ -2.5 is indicative of osteoporosis. Plain radiographs of the hip, including anterior-posterior (AP) views with maximal internal rotation and lateral views, were obtained from all patients. Comparison with the uninvolved hip can be helpful; therefore, an AP pelvis x-ray was frequently obtained. Chest and abdominal x-rays were obtained in all patients. All vertebral fractures were diagnosed as incidental findings on chest or abdominal x-rays.

Exclusion criteria. Exclusion criteria included chronic obstructive pulmonary disease, hematological disorders, autoimmune diseases, valvular diseases, thyroid or parathyroid disorders, rheumatoid arthritis, chronic liver and kidney diseases, fracture, infection, peritonitis, pancreatitis, pelvic inflammatory disease, a recent acute coronary syndrome (< 3 months), cancer, leukocytosis (> 12.000/μl), leukopenia (< 3.500/μl), Cushing syndrome (with dexamethasone suppression tests), fever, and medical treatment with anticoagulant and glucocorticoid (GC) drugs. Patients receiving hormone replacement therapy and antiepileptic medication were also excluded.

Statistical analysis. All data were expressed as means ± SD or percentage. The chi-square statistical test was used for all categorical variables; one-way analysis of variance (ANOVA) was used for all continuous variables. Levene's test was used to assess the homogeneity of variances. Post hoc Tukey tests (for BMI, hemoglobin (HGB), white blood cell (WBC), BUN, creatinine, Ca, total protein, albumin, Na, K, TC, LDL-C, TG, HDL-C, vitamin D, and AST) or Tamhane's T2 tests (for age, NLR, FPG, TSH, and ALT) were used according to homogeneity of variances. Correlations between NLR and clinical parameters were tested by partial correlation. Univariate and multivariate analysis was performed using a linear regression model to determine the relationships between BMD and various clinical variables including age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), TC, TG, HDL-C, LDL-C, and FPG. TG, HDL-C, and FPG were logarithmically transformed before statistical analysis to approximate normal distribution. Statistical significance was defined as p<0.05 (two tailed). The SPSS statistical software package version 17.0 (SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

In this cross-sectional study, 151 patients with osteoporosis, 152 patients with osteopenia, and 135 control subjects were evaluated. Mean age ± SD of subjects were 68 ± 5.6 in the osteoporotic group, 64 ± 6.1 in the osteopenic group, and 60 ± 7.2 in the control group (p<0.001). Demographics and laboratory parameters of the study population are presented in Table 1.

NLR levels of patients with osteoporosis (4.68 ± 0.72) were significantly higher than patients with osteopenia (3.17 ± 0.43) and control subjects (2.01 ± 0.54) (p<0.001) (Fig. 1). After post hoc analysis, there were significant differences between patients with osteoporosis and osteopenia (p=0.001), osteoporosis patients and control subjects (p<0.001), and osteopenia patients and control subjects (p=0.012). CRP levels of osteoporotic patients were significantly higher than those in other groups (p=0.027). After post hoc analysis, significant differences were found between the osteoporosis and osteopenia groups (p=0.014) and the osteoporosis and control groups (p=0.01). The prevalence of CAD was significantly higher in osteoporotic patients than the control group (p=0.008). As BMD decreased, mean age,

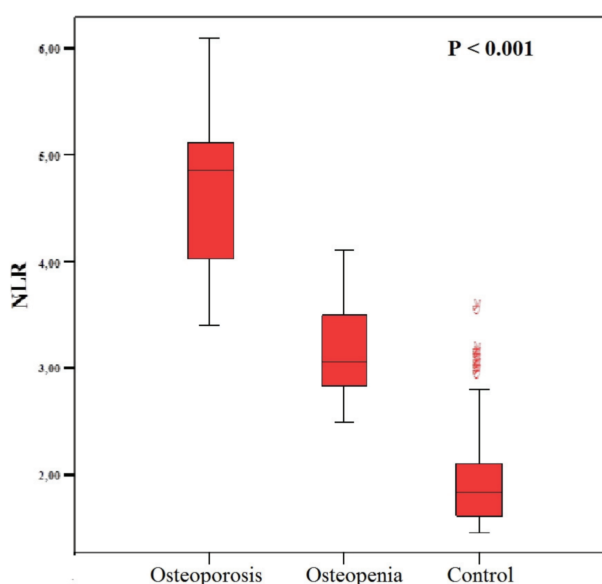

Fig. 1. Comparison of neutrophil-lymphocyte ratio (NLR) in patients with osteoporosis, osteopenia and controls in postmenopausal women.

Table 1

Demographics and laboratory parameters of study population

Variables	Control	Osteopenia	Osteoporosis	p value
Number	135	152	151	
Age years	60 (7.2)	64 (6.1)	68 (5.6)	<0.001
Range	58-75	59-77	60-80	
BMI (kg/m²)	26.5 (3.2)	24.1 (4.1)	22.7 (4.0)	0.001
SBP (mmHg)	15 (16%)	33 (32 %)	53 (48.6)	<0.001
DBP (mmHg)	43 (45.7 %)	59 (57.3 %)	63 (57.8 %)	0.161
Urea (mg/dl)	28 (12)	30 (14)	29 (15)	0.678
Creatinine (mg/dl)	0.85 (0.19)	0.91 (0.20)	0.94 (0.18)	0.348
Ca (mg/dl)	9.1 (1.3)	9.2 (1.4)	8.9 (0.9)	0.217
Total protein (g/dl)	7.1 (1.4)	7.2 (1.3)	7.12 (1.5)	0.765
Albumin (g/dl)	4.2 (0.6)	4.3 (0.5)	4.1 (0.4)	0.801
Na (mEq/l)	138 (3.1)	139 (4.0)	141 (3.9)	0.605
K (mEq/l)	4.1 (0.4)	4.0 (0.5)	3.9 (0.6)	0.576
ALT (U/l)	21 (10)	23 (9)	27 (8)	0.187
AST (U/l)	20 (8)	22 (10)	24 (9)	0.412
TC (mg/dl)	230 (18)	235 (20)	248 (25)	0.014
TG (mg/dl)	210 (32)	258 (32)	279 (28)	<0.001
HDL-C (mg/dl)	44 (12)	41 (14)	32 (16)	<0.001
LDL-C (mg/dl)	140 (18)	156 (21)	158 (23)	0.002
FPG (mg/dl)	102 (12)	107 (14)	113 (18)	<0.001
L2-L4 BMD (g/cm²)	1.098 (0.087)	0.918 (0.123)	0.685 (0.095)	<0.001
T-score L2-L4 (SD)	-0.127 (0.256)	-2.017 (0.727)	-3.812 (0.934)	<0.001
FN BMD (g/cm2)	0.928 (0.191)	0.745 (0.212)	0.632 (0.156)	<0.001
T-score FN (SD)	-0.715 (0.421)	-2.168 (0.381)	-2.956 (0.513)	<0.001
HGB (/µl)	12.1 (1.8)	11.9 (2.0)	10.8 (2.2)	<0.001
WBC (/µl)	6654 (1969)	6731 (2123)	6912 (1954)	0.245
NLR	2.01 (0.54)	3.17 (0.43)	4.68 (0.72)	<0.001
CRP (mg/l)	3.2 (2.1)	4.1 (2.7)	12.3 (4.1)	0.027
DM (%)	38	41	44	0.097
Hypertension (%)	47	49	51	0.619
CAD (%)	17	27	28	0.008
Statins (%)	41	38	42	0.541
Anti-platelets (%)	39	42	41	0.679

Data are expressed as means (SD) or percentage. p value was calculated by one-way analysis of variance (ANOVA) test or chi-square test. BMI – body mass index, SBP – systolic blood pressure, DBP – diastolic blood pressure, Ca – calcium, Na – sodium, K – potassium, ALT – alanine aminotransferase, AST – aspartate aminotransferase, TC – total cholesterol, TG – triglyceride, HDL-C – high density lipoprotein cholesterol, LDL-C – low density lipoprotein cholesterol, FPG – fasting plasma glucose, FN – femoral neck, BMD – bone mineral density, HGB – hemoglobin, WBC – white blood cell, NLR – neutrophil-lymphocyte ratio, DM – diabetes mellitus, CAD – coronary artery disease

SBP, TC, TG, LDL-C, FPG, and NLR increased, while BMI, HDL-C, and HBG decreased. However, DBP and WBC showed no differences. The usage (%) of DM, antihypertensive, anti-platelet, and statin medications showed no differences.

The partial correlation coefficients of NLR and CRP with BMD are presented in Table 2. In model 1, after adjusting for age and BMI, the correlation coefficient between NLR and BMD was -0.411 ($p<0.001$). In model 1, after adjusting for age and BMI, the correla-

Table 2

Partial correlation of NLR, CRP with BMD

Model	Lumbar spine L2-L4		Femoral neck	
	NLR	CRP	NLR	CRP
Model 1a	-0.411*	-0.287*	-0.335*	-0.205*
Model 2b	-0.389*	-0.176*	-0.312*	-0.095
Model 3c	-0.367*	-0.045	-0.298*	-0.031

Abbreviations: see to Table 1. Variables TG, HDL-C, and FPG were log-transformed before statistical analysis. *P<0.001; a – adjusted for age, BMI; b – adjusted for age, BMI, SBP, and DBP; c – adjusted for age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, and FPG

Table 3

Univariate regression analysis with lumbar spine (L2-L4) and femoral neck BMD (g/cm2) as the dependent variables

Variables	Lumbar spine L2-L4 BMD		Femoral neck BMD	
	ß	p value	ß	p value
Age	-0.478	<0.001	0.029	0.703
BMI (kg/m2)	0.219	<0.001	0.041	0.561
SBP (mmHg)	-0.157	0.007	-0.069	0.198
DBP (mmHg)	-0.079	0.173	-0.037	0.631
TC (mg/dl)	-0.272	<0.001	-0.006	0.932
TG (mg/dl)	-0.164	0.001	0.005	0.944
HDL-C (mg/dl)	0.231	<0.001	0.039	0.678
LDL-C (mg/dl)	-0.165	0.018	-0.045	0.497
FPG (mg/dl)	-0.223	<0.001	-0.126	0.015
WBC (/µl)	-0.061	0.345	-0.038	0.713
NLR	-0.432	<0.001	-0.256	<0.001
CRP (mg/l)	-0.152	0.034	-0.043	0.517

Standardized ß regression coefficients. Abbreviations: see to Table 1.

tion coefficient between CRP and BMD was -0.287 (p<0.001). The correlation was similar for NLR but not CRP after adjusting for other risk factors (SBP, DBP, TC, TG, HDL-C, LDL-C, and FPG) in models 2 and 3 (p<0.001). The analysis revealed significant negative associations between NLR and BMD at the lumbar spine (L2-L4) and femoral neck. There is no association between CRP and BMD at the lumbar spine (L2-L4) and femoral neck.

There was a significant correlation between age, SBP, TC, TG, FPG, and NLR (r=0.439, p<0.001 for age; r=0.103, p=0.045 for SBP; r=0.243, p<0.001 for TC; r=0.174, p<0.001 for TG; r=0.154, p=0.001 for FPG). However, there was no significant correlation between BMI, CRP, DBP, LDL-C, and NLR.

Univariate analysis showed that age, BMI, SBP, TC, TG, LDL-C, HDL-C, FPG, CRP, and NLR were significantly associated with lumbar spine (L2-L4) BMD, and that FPG and mean platelet volume (MPV) were significantly associated with femoral neck BMD (Table 3). Multivariate linear regression analysis was performed to assess the relationship between BMD and clinical variables (Table 4). The results revealed that NLR was a significant factor in the multivariate model with BMD. NLR was found to be a significant factor for decreased BMD (ß = -0.285, p<0.001 for lumbar spine (L2-L4) BMD; ß = -0.207, p<0.001 for femoral neck BMD).

Discussion

The main findings of the present study are the following: 1) osteoporosis patients had higher NLR levels in comparison with osteopenic patients and control

subjects; 2) NLR level is tightly correlated with BMD; 3) NLR is an independent variable for predicting the occurrence of osteoporosis; and 4) NLR is better marker than CRP for predicting the occurrence of osteoporosis.

Our study indicated that NLR is increased in the osteoporosis group compared with the osteopenia and control groups. Several mechanisms are potentially responsible for decreased BMD. First, chronic inflammation and estrogen deficiency play pivotal roles in postmenopausal osteoporosis. Osteoporosis is more prevalent in inflammatory conditions such as rheumatoid arthritis, systemic lupus erythematosus (SLE), hematological diseases, inflammatory bowel disease, and other inflammatory diseases, when compared to the healthy population (Mundy 2007). Proinflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-7, IL-11, IL-15 and IL-17 are elevated in these conditions and also in postmenopausal osteoporosis (Weitzmann and Pacifici 2006; Lacativa and Farias 2010). Estradiol (E2) inhibits bone resorption via changes in cytokine and growth factor levels, T cell activation, and oxygen radical production (Weitzmann and Pacifici 2006; Zhao 2012). Most of the estrogenic effects of E2 on bone cells are mediated via estrogen receptor alpha (ERα) (Straub 2007), and E2 induces osteoclast apoptosis while inhibiting osteoblast apoptosis (Straub 2007; Bhat et al. 2013). E2 deficiency leads to up-regulation of cytokines such as IL-1, IL-7, TNF-α, interferon (IFN)-γ, and IL-6, which contribute to the activation of osteoclasts (Jilka et al. 1992; Weitzmann and Pacifici 2006). Particularly, TNF from T cells is an important cofactor in bone resorption because this cytokine supports osteoclast activation mediated by the system of receptor activator of RANK)/RANKL and c-Fms/macrophage colony stimulating factor (Mundy 2007; Lacativa and Farias 2010; Bhat et al. 2013). Estrogen is able to suppress the production of these proinflammatory cytokines and stimulate production of osteoprotegerin (OPG) (Straub 2007). Studies on bone resorption demonstrated that estrogen deficiency following menopause resulted in an increase in these cytokines and simultaneously led to downregulation of OPG, resulting in local inflammation in the bone (Weitzmann and Pacifici 2006). Hence, it is suggested that estrogen deficiency can be associated with an increase in production of proinflammatory cytokines, which in turn increases osteoclastic activity, resulting in profound bone loss. Therefore, osteoporosis can be strongly associated with inflammation. In this study, high NLR is a biomarker of chronic active inflammation that also predicts postmenopausal osteoporosis.

Table 4

Stepwise multivariate linear regression analysis with lumbar spine (L2-L4) and femoral neck BMD (g/cm2) as the dependent variables

Variables	ß	p value
Model A		
NLR	-0.653	<0.001
Age (years)	-0.436	<0.001
BMI (kg/m²)	0.253	0.010
FPG (mg/dl)	-0.105	0.025
Model B		
NLR	-0.178	<0.001

Standardized ß regression coefficients. p value for entry was set at 0.05 and p value for removal was set at 0.10. For model A, lumbar spine L2-L4 BMD as the dependent variable; for model B, femoral neck BMD as the dependent variable.
Abbreviations: see to Table 1

Second, endogenous glucocorticoid (GC) production and sensitivity to the effects of GCs increase with age and menopause, inexorably contributing to the effects of old age in the development of osteoporosis (Weinstein 2011). Endogenous GCs may participate in bone physiology, even in subjects with normal GC levels. This is mainly based on the finding that circulating GC levels are significantly associated with BMD in healthy men and women (Dennison et al. 1999; Cooper et al. 2005). Importantly, bone tissue-specific response to GC appears strongly correlated with serum levels of cortisone but not cortisol (Pierotti et al. 2008), suggesting the presence of a local activator regenerating the natural ligand of GC receptor (GR) at the bone level to produce the observed biological effects. This enzyme, 11beta-hydroxysteroid dehydrogenase type 1 (11β-HSD1), activates GCs and is expressed in human osteoblasts in vivo (Cooper et al. 2000). Increasing 11β-HSD1 activity is implicated in age-related bone loss (Cooper et al. 2002). In both age-related and pharmacologic hyperglucocorticoidism, increased apoptosis of osteocytes and decreased insulin-like growth factor-I levels contribute to the decrease in bone-forming cells (Dennison et al. 1999). GC promotes the expression of a receptor/activator of the NFκB ligand and decreases osteoprotegerin expression in osteoblasts, thus stimulating osteoclastic bone resorption (Weinstein 2011). Additionally, GC suppresses intestinal absorption of calcium and gonadal hormones (Weinstein 2011). Andersson et al. (2010)

showed that estrogen reduced 11β-HSD1 in a rat model. Yamatani et al. (2012) reported a significant correlation between the cortisol/cortisone ratio and the E1/E2 ratio of visceral fat in postmenopausal women (Yamatani et al. 2012). The effects of estradiol on the 11β-HSD1 are diverse and may be species- and tissue-specific. Yet, our hypothesis stated that in the postmenopausal phase, E2 deficiency induces 11β-HSD1 activity in bone, therefore, relative hyperglucocorticoidism also contributes to postmenopausal osteoporosis. Cortisol decreases neutrophil adhesion to endothelial cells, resulting in a neutrophilic leukocytosis; increased adhesion of lymphocytes in efferent lymphatics produces lymphopenia. Relative hyperglucocorticoidism may be associated with high NLR in postmenopausal osteoporosis.

In our study, we found that osteoporotic and osteopenic women have higher instances of CAD than control subjects. Evidence from population and clinical studies suggests that a relationship exists between cardiovascular diseases and low bone mineral density (Varma et al. 2008). Recently, Qu et al. (2011) performed a meta-analysis of prospective cohort studies, showing that lower BMD is associated with a significantly increased risk of all-cause and cardiovascular mortality. The association between atherosclerosis and osteoporosis can be explained by several etiologic factors and mechanisms. First, aging and menopause (estrogen deficiency) are common clinical features for both conditions. In particular, ERs have been identified in bones (osteoclasts and osteoblasts) (Straub 2007) and blood vessels (endothelial and smooth muscle cells) (Straub 2007), suggesting that estrogen may directly regulate bone metabolism and have clinical importance for atherosclerosis. The prevalence of osteoporosis and CAD are related to the coexistence of risk factors, including inactivity, smoking, low vitamin D concentrations, hypertension, alcohol abuse, type II DM, and dyslipidemia (Varma et al. 2008). Chronic inflammation, oxidative stress, and altered homocysteine levels are also risk factors for both conditions (Hofbauer et al. 2007; Varma et al. 2008). In addition, drugs that are used for hypertension and hyperlipidemia increase BMD (Edwards et al. 2000; Lynn et al. 2006) and bisphosphonates reduce CAD risk (Price et al. 2001). Several bone-related proteins such as osteoprotegerin, osteopontin, osteonectin, matrix Gla protein, and bone morphogenetic protein are demonstrated in arteries with atherosclerosis, implying a possible molecular link between the two diseases (Hofbauer et al. 2007).

We demonstrated that NLR is better predictor than CRP for occurrence of postmenopausal osteoporosis. In addition, NLR correlated more closely than CRP with BMD. Four cross-sectional studies have analyzed the relationship between CRP and BMDs (Ganesan et al. 2005; Koh et al. 2005; Bhupathiraju et al. 2007; de Pablo et al. 2012). Two of these previous studies (Ganesan et al. 2005; Bhupathiraju et al. 2007) showed that CRP was not associated with bone mass in healthy postmenopausal women after multivariate analysis. However, in a cross-sectional study, Koh et al. (2005) showed that higher serum high-sensitivity (hs)CRP levels were associated with lower BMD in a large population of Korean women. As a limitation of this study, the study population was comprised of women who visited a health promotion center, and may not have been representative of the general population residing in a community, thus possibly resulting in selection bias. Recently, de Pablo et al. (2012) showed that the CRP level was inversely and independently associated with total BMD. Our results are consistent with the other previous studies (Ganesan et al. 2005; Bhupathiraju et al. 2007). This study showed an unsimilar finding according to de Pablo et al. (2012). The association between CRP and BMD became statistically insignificant after adjustment for age, BMI, SBP, DBP, TC, TG, HDL-C, LDL-C, and FPG. We explained these results: first, de Pablo et al. (2012) performed a multiethnic population study with adjustments only for age, comorbidities, and drugs. We suggest that these adjustments are not enough to define the association between BMD and CRP. Their study population has higher mean age than our population. But our study includes a relatively small number of subjects and strict exclusion criteria, and we examined only postmenopausal women. We assayed serum CRP, which may not change in the microenvironment of bone, and this could be another factor in the differing results.

There were several potential limitations to this study. First, because this was a cross-sectional study, we cannot determine if there is a causal relationship between NLR, CRP levels and BMD values. Further prospective studies are necessary to determine whether this correlation is reflective of a causal relationship. Second, results were dependent on single occasion instead of serial measurements, so laboratory measurement errors could have affected the accuracy of data. Third, the study is lacking information about the biochemical markers of inflammation (such as IL-1, IL-6, IL-11, IL-17, and TNF-α), hormones (E1, E2, cortisol, and cortisone), and bone-related proteins (such as osteoprotegerin,

osteopontin, osteonectin, matrix Gla protein, and bone morphogenetic protein). This information could provide additional information about the pathway underlying high NLR levels.

In conclusion, NLR is a better predictor than CRP for postmenopausal osteoporosis. The present study demonstrates, for the first time that NLR levels are significantly elevated in postmenopausal osteoporosis and are correlated with BMD. If this data can be confirmed with further trials, we believe that a standardized cut-off value for NLR would facilitate the diagnosis of postmenopausal osteoporosis. We therefore suggest that NLR, as an inexpensive and simple test, is a valuable tool for occurrence of osteoporosis in postmenopausal women.

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