Evaluation of Bone Mineral Density, Hormones, Biochemical Markers of Bone Metabolism, and Osteoprotegerin Serum Levels in Patients with Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To evaluate bone metabolism in patients with ankylosing spondylitis (AS) and test the hypothesis that osteoprotegerin (OPG) serum concentrations are correlated with the severity of bone loss as assessed by bone mineral density (BMD) and biochemical markers of bone turnover. Osteoporosis occurs frequently in patients with AS and OPG represents a soluble decoy receptor that neutralizes receptor activator of nuclear factor-κB ligand (RANKL), an essential cytokine for osteoclast function.

Methods. Clinical data, radiographs of the spine, BMD of lumbar spine and the femur, biochemical markers of bone turnover, and serum levels of OPG were evaluated in 264 patients with AS (72% men) and 240 age-matched healthy controls (76% men).

Results. OPG serum levels were significantly lower in patients with AS compared to controls (1.84 ± 1.15 vs 3.54 ± 2.18 pmol/l, $p < 0.001$), and in contrast to controls, were not positively correlated with age. In addition, BMD of the hip and the femoral neck were significantly lower in patients with AS than in controls. There were positive correlations in patients with AS between BMD of the femoral neck and free testosterone serum levels in men and free estradiol serum levels in women, respectively. Patients with AS and osteoporosis had higher biochemical markers of bone resorption and inflammatory activity.

Conclusion. Bone loss in patients with AS is associated with low sex steroid hormone serum levels, high biochemical markers of bone resorption and inflammatory activity, low OPG serum levels, and lack of compensatory age-related increase of OPG serum levels. (J Rheumatol 2004;31:2236–41)

Key Indexing Terms:
OSTEOPROTEGERIN ANKYLOSING SPONDYLITIS OSTEOPOROSIS

Osteoporosis is a frequent complication of ankylosing spondylitis (AS), yet its pathogenesis has not been well defined[1-3]. Osteoporosis may be suspected radiographically, but the presence of syndesmophytes and ankylosis may hamper its diagnosis. Consequently, the degree of osteopenia or osteoporosis may be difficult to assess by bone mineral density (BMD) measurements[4-6]. Furthermore, the role of bone turnover in AS is controversially discussed[7,8], with some studies indicating reduced or increased biochemical markers of bone turnover[7-12].

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Osteoprotegerin (OPG) is ubiquitously produced by a variety of tissues, cell types, and cell lines[13-15]. OPG binds and neutralizes receptor activator of nuclear factor-κB ligand (RANKL), and thus prevents RANKL activation of receptor activator of nuclear factor-κB (RANK)[16-19]. *In vivo*, overexpression of OPG in transgenic mice[13] or administration of OPG to normal rodents[13,14] inhibited osteoclastogenesis, osteoclast activation, and bone resorption, resulting in osteopetrosis. Because activated T cells produce RANKL, and RANKL regulates important functions of osteoclast cells (which express RANK), the RANKL/RANK/OPG system may play an important role in the pathogenesis of inflammatory bone diseases[20].

We tested the hypothesis that OPG serum concentrations are different between patients with AS and controls and are associated with skeletal abnormalities in AS. We evaluated whether OPG serum concentrations were correlated with changes in biochemical markers of bone turnover or BMD in patients with AS.

MATERIALS AND METHODS

Patients and controls. We studied 264 patients with AS, 190 men (mean

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age 50.4 ± 10.4 yrs, range 27 to 75 yrs) and 74 women (57% pre-, 43% postmenopausal, mean age 48.0 ± 11.1 yrs, range 26 to 78 yrs) attending our Center of Rheumatology in Oberammergau, Germany. All patients fulfilled the diagnostic criteria for AS defined by the modified New York criteria[21]. Patients with psoriatic arthritis, reactive arthritis, or inflammatory bowel or other diseases affecting bone metabolism were excluded. A total of 240 healthy volunteers served as controls, 182 men (mean age 50.4 ± 14.6 yrs, range 19 to 77 yrs) and 58 women (mean age 48.1 ± 9.7 yrs, range 17 to 64 yrs) who lacked clinical signs and symptoms of inflammatory joint diseases or bone diseases and were not taking drugs known to affect bone metabolism. No patient had received glucocorticoids or disease-modifying antirheumatic drugs for the previous 12 months and no patient had a history of longterm glucocorticoid therapy. Two hundred twenty-seven patients (86%) took nonsteroidal antiinflammatory drugs (NSAID) within the last 12 months. All participants provided written informed consent to participate in this study.

Clinical examination. Clinical examination was performed by the same experienced rheumatologist (HF) to avoid interobserver variation. Cervical rotation was measured with a goniometer; lateral spinal flexion was measured by finger tip-to-floor distance in full lateral flexion without flexing forward or bending the knees. Lumbar flexion was assessed by the Schober index. In addition, chest expansion, body mass index (BMI), cervical side flexion, and vital capacity were measured. All patients completed the Bath AS Disease Activity index (BASDAI)[22] and the Bath AS Functional Index (BASFI)[23].

Radiological studies. In all patients, anterior, posterior, and lateral radiographs of the lumbar, thoracic, and cervical spine were performed. The New York criteria were used to score sacroiliac joints[21]. Syndesmophytes were scored as 0, normal; 1, without fusion; and 2, with fusion for each vertebra of the spine. To assess radiological involvement, the Bath AS Radiology Index (BASRI)[24] was used.

Assessment of BMD. BMD of the lumbar vertebrae and different sites of the right femoral region (femoral neck, Ward's triangle, inter-trochanter, total) was measured by dual-energy x-ray absorptiometry (DEXA) using the Hologic QDR 4500 device. *In vitro* precision was 0.9%, *in vivo* precision errors were less than 1.5% at the lumbar spine and less than 1.0% at the hip[25,26]. Osteopenia and osteoporosis were defined according to the criteria of the World Health Organization.

Evaluation of biochemical markers of bone turnover. All urine and blood samples from our patients were taken between 8:30 AM and 9:30 AM after an overnight fast. After centrifugation, serum samples were stored at –70°C prior to analysis. Bone-specific alkaline phosphatase activity was determined in serum by an immunoassay (Olympus Diagnostica, Hamburg, Germany) (interassay coefficient of variation, CV: 6.9%; intraassay CV: 1.4%). Serum levels of intact parathyroid hormone were measured by a 2-site immunometric assay (Nichols Diagnostics, Bad Nauheim, Germany) (interassay CV: 11%; intraassay CV: 7.9%). Serum levels of

25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 were measured by commercial radioimunoassays (Nichols Diagnostics, Bad Nauheim, Germany and Dia Sorin, Brussels, Belgium) (interassay CV: 6.6% and 7.7%, respectively; intraassay CV: 11% and 4.3%, respectively). Testosterone and 17ß-estradiol serum levels were measured using radioimmunoassays (Bayer/Centaur, Berlin and Biochem-Maia, Fernwald, Germany) (interassay CV: 6.8% and 5.5%, respectively; intraassay CV: 4.7% and 3.0%, respectively). Sex-hormone binding globulin serum levels were determined by an immunoradiometric assay (DPC Biermann, Bad Nauheim, Germany) (interassay CV: 6.3% and intraassay CV: 13%). Urinary excretion of pyridinoline and deoxypyridinoline were measured by high performance liquid chromatography (HPLC) (interassay CV: 9.3% and 4.2%, respectively). Erythrocyte sedimentation rate (ESR) was determined using the Westergren method, and C-reactive protein (CRP) was measured using a non-sensitive commercial assay (Tina-quant CRP) (Roche Diagnostics, Mannheim, Germany).

Measurement of osteoprotegerin serum concentrations. OPG serum concentrations were determined using an immunoassay (Immunodiagnostik, Bensheim, Germany) as described[27]. Measurements were performed in undiluted samples according to the manufacturer's instructions. The lower limit of detection of this assay is 0.14 pmol/l with intraassay CV (n = 16) of 9.0%.

Statistical analysis. Statistical analysis was performed with SPSS 10.0 software (SPSS, Chicago, IL, USA). Descriptive statistics were calculated for all groups. Correlations are presented as Spearman correlation and partial correlation coefficients. The main demographic characteristics of the AS group and controls were compared using Student's t test. P values < 0.05 were considered statistically significant.

RESULTS

Table 1 summarizes the clinical data of patients with AS and controls. OPG serum levels were significantly lower in patients with AS versus controls, in both men and women. While OPG serum levels were positively correlated with age in the control group ($r = 0.48$, $p < 0.01$), there was no such correlation in patients with AS ($r = 0.02$, $p = 0.75$).

In women with AS, OPG serum levels were comparable before (n = 42; 1.81 ± 1.23 pmol/l) and after menopause (n = 32; 1.70 ± 0.99 pmol/l; NS) (Figure 1), although OPG serum levels were negatively correlated with serum levels of estradiol ($r = –0.29$, $p < 0.05$). In men, OPG serum levels were not correlated with lumbar spine BMD ($r = 0.061$, $p = 0.433$), total hip BMD ($r = –0.28$, $p = 0.722$), or femoral neck BMD ($r = –0.037$, $p = 0.637$), urinary excretion of pyridinoline ($r = 0.051$, $p = 0.509$), or deoxypyridinoline cross-links ($r = –0.43$, $p = 0.579$). OPG serum levels were not significantly different in patients with AS using (2.09 ± 1.28 pmol/l) compared to those not using NSAID (1.81 ± 1.14 pmol/l, NS).

Patients with AS presented with significantly lower BMI, and reduced mobility of the cervical, thoracic, and lumbar spine, as assessed by anterior and lateral flexion and rotation. Furthermore, both men and women with AS showed a significant loss of height and an increased BASRI score. In contrast to lumbar spine BMD, total hip BMD ($p < 0.01$), and femoral neck BMD ($p < 0.001$) were significantly lower in women and men with AS than in controls (Table 2). Of note, BMD at the lumbar spine and the total hip were similar in patients with AS regardless of NSAID use.

In our cohort, 41 patients with AS had appendicular involvement, while the majority (n = 223) had no appendicular involvement. In patients with AS, OPG serum levels were similar in patients with (1.89 ± 1.29 pmol/l) or without appendicular involvement (1.83 ± 1.13 pmol/l, NS). In addition, BMD values were similar in AS patients with (lumbar spine 1.09 ± 0.31; total hip 0.91 ± 0.15) or without appendicular involvement (lumbar spine 1.03 ± 0.23; total hip 0.92 ± 0.14, NS).

In men with AS, serum levels of testosterone (4.5 ± 1.7 vs 3.9 ± 1.2 µg/l, $p < 0.05$) were slightly higher than in controls, but mean values were within the normal range. In patients with AS, men with osteoporosis had significantly

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Table 1. Clinical characteristics of patients with AS and controls.

Variables	Men				Women			
	AS		Controls		AS		Controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of patients	190		182		74		58	
Age, yrs	50.4	10.4	50.4	14.6	48.0	11.1	48.1	9.7
Chest expansion, cm	2.5***	1.3	5.1	0.8	3.3***	1.4	5.0	0.3
Lumbar Schober, cm	11.5***	2.1	14.2	1.4	12.3***	2.8	14.3	0.8
Thoracic Schober, cm	30.6*	2.8	32.0	3.7	31.4***	0.9	32.7	0.6
Finger to floor ventral, cm	25.7*	14.0	17.8	15.7	16.9	15.0	13.3	15.3
Lateral flexion right, cm	7.6*	4.8	22.0	0.5	10.2**	5.7	16.1	4.8
˚CS Rotation right	42.2***	21.7	69.7	13.7	55.0***	20.9	72.8	12.7
˚CS side-shift right	15.0**	10.6	19.5	6.7	21.4	10.5	22.5	5.7
Loss of height, cm	3.9***	3.4	0.5	1.0	3.0***	4.0	0.5	1.6
BASRI spine	8.8	2.9	NA	NA	6.1	3.5	NA	NA
BASDAI	4.3	1.9	NA	NA	4.6	1.6	NA	NA
BASFI	4.3	2.0	NA	NA	4.2	2.0	NA	NA

CS: cervical spine; LS: lumbar spine; BASRI: Bath AS Radiology Index; BASDAI: Bath AS Disease Activity Index; BASFI: Bath AS Functional Index; NA: not applicable. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

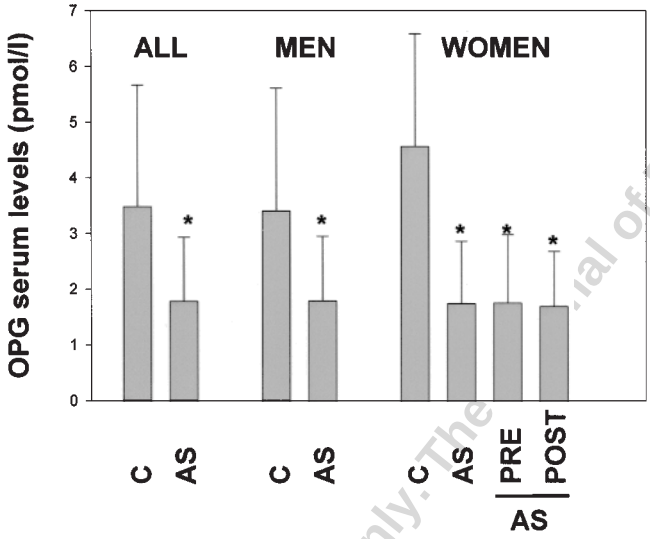

Figure 1. Osteoprotegerin serum levels in patients with ankylosing spondylitis and controls (*p < 0.001 vs controls). C: controls; AS: ankylosing spondylitis; PRE: premenopausal women with AS; POST: premenopausal women with AS.

lower serum levels of free testosterone (0.15 ± 0.05 vs 0.18 ± 0.08 µg/nmol, $p < 0.05$) and women with osteoporosis had significantly lower serum levels of estradiol (23.5 ± 34.4 vs 80.9 ± 72.2 ng/l, $p < 0.01$) than those without osteoporosis, although sex steroid hormones were within normal limits. In women with AS, BMD at the femoral neck was positively correlated with serum levels of estradiol ($r = 0.37$, $p < 0.01$) and negatively with urinary excretion of deoxypyridinoline cross-links ($r = –0.38$, $p < 0.01$) and the BASRI of the spine ($r = –0.40$, $p < 0.01$).

Of note, patients with AS (Table 3) had increased inflammatory activity measured by CRP and ESR and increased serum levels of vitamin D. Men, but not women, with AS had increased bone resorption markers (urinary excretion of deoxypyridinoline and pyridinoline). In patients with AS, CRP levels were positively correlated with urinary excretion of deoxypyridinoline ($r = 0.20$, $p < 0.01$) and pyridinoline ($r = 0.35$, $p < 0.01$) crosslinks and negatively with serum levels of estradiol ($r = –0.13$, $p < 0.05$). Analysis of clinical and laboratory variables and the BMD of the femoral neck revealed that men and women with AS and osteoporosis had a reduced function of the spine (reclination of cervical spine: 9.8 ± 5.7 vs 12.8 ± 4.9 cm, $p < 0.01$; lumbar Schober: 10.8 ± 2.0 vs 12.3 ± 2.7 cm, $p < 0.001$), higher urinary excretion of pyridinoline (295 ± 143 vs 252 ± 74 µg/g creatinine, $p < 0.05$) and ESR (17 ± 12 vs 12 ± 12 mm/h, $p < 0.05$) than patients with normal BMD. In addition, we found significantly lower serum levels of vitamin D (17.3 ± 5.9 vs 26.9 ± 12.8 µg/l, $p < 0.05$) and estradiol (23.5 ± 34.4 vs 80.9 ± 72.2 ng/l, $p < 0.01$) in women with AS and osteoporosis.

DISCUSSION

Using a large and well-characterized cohort of 264 patients with AS, we found evidence that bone loss in patients with AS is associated with low serum levels of sex steroid hormones, high biochemical markers of bone resorption and inflammatory activity, low OPG serum levels, and lack of compensatory age-related increase of OPG serum levels. Our data regarding low OPG serum levels in patients with AS are consistent with data obtained in patients with rheumatoid arthritis (RA), in which the findings of low OPG serum levels were considered inappropriately low to counteract enhanced bone resorption[28]. In contrast to our findings, OPG serum levels were found to be increased in 2

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Table 2. Bone mineral density (g/cm^2) of lumbar spine and hip in patients with AS and controls.

	Men				Women			
	AS		Controls		AS		Controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of patients	190		182		74		58	
BMD LS total	1.05	0.26	1.03	0.13	1.01	0.18	1.04	0.14
LS total T-score	–0.55	1.64	–0.53	1.22	–0.32	1.65	–0.17	1.35
BMD of the hip total	0.94**	0.14	1.01	0.12	0.87**	0.13	0.95	0.14
Hip total T–score	–1.13**	1.06	–0.49	0.93	–0.89*	1.07	–0.40	1.20
BMD of femoral neck	0.57	0.13	0.63	0.15	0.61*	0.16	0.69	0.20
Femoral neck T-score	–1.71*	1.09	–1.09	1.18	–1.14	1.33	–0.72	1.38

BMD: bone mineral density; LS: lumbar spine. * $p < 0.05$; ** $p < 0.01$.

Table 3. Laboratory variables of patients with AS and controls.

	Men				Women			
	AS		Controls		AS		Controls	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Number of patients	190		182		74		58	
OPG, pmol/S	1.85***	1.16	3.46	2.21	1.80***	1.12	4.62	2.02
ESR, mm/h, S	13.9***	12.9	5.7	3.4	15.2**	11.6	9.5	9.2
CRP, mg/dl, S	1.5***	2.1	0.1	0.5	1.1**	1.8	0.4	1.1
AP bone, U/I, S	18.6	6.2	19.2	6.7	14.7**	4.7	19.0	7.9
Phosphate, mg/dl, S	3.3	0.5	3.3	0.5	3.7	0.4	3.8	0.4
Deoxypyridinoline, µg/g Cr, U	42.6**	14.8	35.9	9.7	49.0	19.6	48.0	24.5
Pyridinoline, µg/g Cr, U	258.8**	91.8	226.6	48.3	283.2	105.9	294.7	123.2
25-Vitamin D_3, µg/l, S	21.1**	10.5	14.2	8.7	23.4**	11.3	18.0	10.4
1,25-Vitamin D_3, ng/l, S	45.0*	14.7	55.5	22.2	43.6*	16.4	36.9	14.0
Estradiol, ng/l, S	15.4	12.1	16.4	4.8	53.5*	60.0	31.1	38.4
Testosterone, µg/l, S	4.5*	1.7	3.9	1.2	0.2*	0.1	0.3	0.2
SHBG, nmol/l, S	31.0	13.2	27.0	10.9	70.3	47.1	54.5	55.2
T/SHBG, µg/nmol, S	0.159	0.066	0.150	0.046	0.004**	0.004	0.008	0.008
Parathyroid hormone, ng/l, S	26.2	13.6	30.6	16.1	28.5	18.9	28.9	14.1

OPG: osteoprotegerin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; AP: alkaline phosphatase; Cr: creatinine. SHBG: sex-hormone binding globulin; T: testosterone. S: serum; U: urine. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

smaller studies with cohorts of 25 and 30 patients with AS[29,30]. The first study was conducted in Austria involving 30 patients with a similar sex and age distribution, although BASFI and BASDAI were not described[29]. Urinary excretion of pyridinoline and deoxypyridinoline was increased in AS, consistent with our study, while no differences for vitamin D or sex hormone levels were found. The second study was from Brazil involving 25 patients (with fewer women) at a younger age, a longer duration of disease, and higher BASFI (5.5) and BASDAI (4.7) scores[30]. In addition, 92% of patients had peripheral involvement, indicating a more severe course of AS. While no information on medications or hormones was available, urinary deoxypyridinoline levels were lower in AS patients[30].

An important feature of OPG regulation *in vivo* is a significant increase of OPG serum levels with ageing in healthy persons and patients with osteoporosis[27,31,32]. This pattern, which was confirmed in our control group, has been viewed as a compensatory mechanism to prevent further bone loss. In this regard, the fact that there was no age-related increase of OPG serum levels in patients with AS may indicate an important impairment in the capacity to counterbalance enhanced bone loss in AS.

Assessment of BMD in patients with AS showed a high prevalence of osteopenia or osteoporosis at the hip both in women and men[2,33]. While BMD at the hip was positively correlated with serum levels of free estradiol and negatively with deoxypyridinoline crosslinks in women, it was positively correlated with serum levels of free testosterone and negatively with parathyroid hormone in men. This may indicate gender differences in the pathogenesis of bone loss associated with AS. Our data confirm that OPG serum levels were not correlated with BMD at the lumbar spine[27,31,34,35].

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In men, testosterone serum levels were higher in patients with AS than healthy men, but in men with AS, those with osteoporosis had lower testosterone serum levels than non-osteoporotic men, consistent with the known effect of testosterone in the pathogenesis of male osteoporosis. However, these changes were subtle, consistent with the notion that adrenal or gonadal hormones are not severely altered in AS[36]. Probably, because of the low incidence of AS in women, data on the role of estrogen levels in the pathogenesis of bone loss in AS are limited. While vitamin D levels were slightly higher in women and men with AS compared to healthy controls, they were within the upper normal range. This has been previously reported in a smaller cohort of patients with AS unrelated to this cohort[7]. Taken together, subtle abnormalities of sex steroid hormones, parathyroid hormone, and vitamin D are potential endocrine mechanisms that contribute to the pathogenesis of bone loss associated in AS.

Abnormalities of proinflammatory cytokines and alterations of the RANKL/OPG system have been described in patients with RA and are associated with enhanced bone resorption[37,38]. Similar to RA, previous studies indicated that bone loss in AS was associated with enhanced inflammatory activity[33] and increased bone resorption[39,40]. Our data support those findings. Patients with AS had higher serum levels of CRP and urinary excretion of crosslinks than controls, and among patients with AS, patients with low BMD had higher ESR and higher urinary excretion of crosslinks than those with normal BMD. Enhanced CRP levels have been reported in patients with active AS[29,41], but were not correlated with OPG serum levels in our cohort. Consistent with this, the use of NSAID was not associated with altered OPG serum levels or BMD measurements in patients with AS.

In summary, bone loss in patients with AS is associated with low serum levels of sex steroid hormones, high biochemical markers of bone resorption and inflammatory activity, low OPG serum levels, and lack of compensatory age-related increase of OPG serum levels.

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