

The relation between osteoporosis and vitamin D levels and disease activity in ankylosing spondylitis

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Abstract In this study, the relation between osteoporosis and vitamin D and the disease activity in patients with ankylosing spondylitis (AS) was investigated. A hundred patients with AS and 58 healthy individuals were included in the study. In addition to the routine blood and urine tests, serum 25-(OH)D₃, parathormone (PTH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), total calcium, ionized calcium, and phosphorous levels of all participants were also measured. Bone mineral density (BMD) measurements were performed at the anterior–posterior and lateral lumbar and femur regions. Anterior–posterior and lateral thoracic and lumbosacral radiography was performed on all participants. The disease activity was evaluated by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), functional status by Bath Ankylosing Spondylitis Functional Index (BASFI), and mobility by Bath Ankylosing Spondylitis Metrology Index (BASMI). In the patient group, BMD values obtained from the lateral lumbar and femur regions and serum vitamin D levels were lower than the control group. A negative relation was determined between the lateral lumbar BMD values and ESR, CRP, and BASDAI scores of patients with AS. The ESR, CRP levels, and BASMI scores of the AS patients with osteoporosis were significantly higher, when compared to patients without osteoporosis. The negative correlation between serum 25-(OH)D₃ level and ESR, CRP levels did not reach a statistically significant level in patients with AS; the positive correlation between PTH

levels and ESR, and the negative correlation between CRP and BASDAI also did not reach a statistically significant level. Vitamin D deficiency in AS may indirectly lead to osteoporosis by causing an increase in the inflammatory activity. The present authors believe that it would be beneficial to monitorize vitamin D levels together with BMD measurements in order to determine the patients under osteoporosis risk.

Keywords Ankylosing spondylitis · Osteoporosis · Vitamin D · Inflammatory activity

Introduction

Ankylosing spondylitis (AS) is a chronic, systemic, and inflammatory disease that characteristically involves the axial skeleton, entheses regions, and in some patients the peripheral joints [1]. In the pathology of AS, inflammation and ossification play a primary role together and cause new bone formations in the spine and ankylosis. Also, osteoporosis accompanies these findings from the early stages of the disease, but the etiology of osteoporosis has not yet been completely clarified. It is thought that the immobilization and not using the spine due to spinal pain and/or movement restriction is causative factors in the development of osteoporosis [2]. Besides, medications used for treatment, hormonal disorders, and genetic factors also contribute to the development of osteopenia/osteoporosis. The relation between inflammatory activity and the loss of bone mass developing at a significant rate during the early stages of disease has been demonstrated [3–5].

It is suggested that high levels of proinflammatory cytokines, known to play a major role in chronic inflammation are also effective on osteoblasts and osteoclasts. It

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is thought that the inflammatory activity in AS also plays an important role in the pathophysiology of bone loss, this role being controlled by the substances that regulate both the inflammatory process and the bone turnover [6–9]. Another factor that is effective on the development of osteoporosis in AS is vitamin D. It was demonstrated that in patients with AS, the high disease activity was related with the alterations in vitamin D metabolism and increased bone resorption [4, 5]. It is also known that vitamin D plays a regulatory role on the immune system both at the cellular level and by the mediation of cytokines [10–15].

In this study, the relation between disease activity and osteoporosis and vitamin D levels in patients with AS was investigated.

Materials and methods

A hundred patients with the diagnosis of AS (75 males, 25 females) according to the Modified New York Criteria [16] and 58 healthy individuals (46 males, 12 females) as the control group were included in the study. The patients and the healthy individuals were informed about the study and informed consent was taken. The approval of the ethics committee was taken.

In the patient group, age, gender, occupation, educational status, duration of disease, peripheral joint involvement, extra-articular involvement, family history, the presence or absence of diabetes, hepatic and renal diseases, and history of operations were recorded.

The exclusion criteria for the patient and the control group were determined as associating inflammatory intestinal disease (Crohn's disease, ulcerative colitis), malnutrition, hyperparathyroidism, hyperthyroidism, renal and hepatic disease, and medications that might affect bone metabolism and the endocrine system (such as thyroxin, anticonvulsants, glucocorticoids, hormone replacement therapy). The individuals with any inflammatory rheumatic disease were not included in the control group. All patients with AS and the control group were physically active for the last 12 months. All female individuals were in the premenopausal period. The individuals with a history of nonvertebral osteoporosis related fracture were not included in the study.

In the patient group, medication history was recorded. In order to determine the level of disease activity, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used [17]. With the aim of identifying the patients' functional levels, they were asked to complete the questionnaire of Bath Ankylosing Spondylitis Functional Index (BASFI) [18]. The validity and reliability of the Turkish versions of these forms have been approved [19, 20].

Heights and body weights of the patient and the control groups were measured and recorded and then their body

mass indexes (BMI) were calculated. The physical examinations of the patients were performed and their spinal mobility was evaluated. For mobility evaluation, the criteria of Bath Ankylosing Spondylitis Metrology Index (BASMI) were used [21].

Laboratory analysis

Intact PTH ($n = 1.6$ – 6.9 pmol/l), bone-specific alkaline phosphatase (bone ALP, $n = 9$ – 116 IU/l), 25-(OH)D3 ($n = 20$ – 120 mmol/l) levels in the patient and the control groups were analyzed with standard methods. Also, C-reactive protein (CRP) with the nephelometric method ($n = 0$ – 5.0 mg/l), erythrocyte sedimentation rate (ESR) with the Westergren method, serum total calcium, ionized calcium, urea, creatinine, phosphorous, ALT, AST, total protein, and albumin levels were measured with the standard autoanalyzer.

Radiologic examinations and BMD measurement

In all participants, plain radiographs of lumbar and thoracic vertebrae in lateral and anterior–posterior aspects were taken. All radiographs were evaluated by one radiologist and vertebral fractures were diagnosed by quantitative assessment method. According to this, if the height of the anterior, posterior, or mid-vertebra had decreased by least 15%, vertebral fracture would be diagnosed [22, 23].

Bone mineral density (BMD) of all participants was measured at the anteroposterior lumbar 1–4th, lateral lumbar 2–3rd vertebrae and femur neck, Ward's triangle, and total hip regions with the Hologic Discovery W series DEXA device and the results were evaluated as g/cm^2 .

Statistical analysis

All data were analyzed by SPSS 13.0 software. With the aim of evaluating the differences between groups, Student's *t* test for the variables with a normal distribution and nonparametric Mann–Whitney *U* test for the variables with abnormal distribution were used. While studying the relations between the variables in the patient group, Pearson correlation test was used for parametric variables and Spearman correlation test was used for nonparametric variables. A *P* value of <0.05 was accepted as statistically significant.

Results

In this study, there were a total of 100 patients, 75 males and 25 females in the patient group and a total of 58 individuals, 46 males and 12 females, in the control group.

The mean age of the patients was 39.9 ± 10.9 years old and the mean age of the control group was 38.1 ± 9.6 years old. The mean BMI of the patients was 26.05 ± 4.38 kg/cm² while being 25.90 ± 4.50 kg/cm² in the control group. No statistically significant difference was detected between groups in terms of age, gender distribution, and BMI ($P > 0.05$). In the patient group, duration of disease ranged between 6 months and 40 years (average 10.50 ± 7.84 years). Extra-articular involvement was present at 27 patients and in 49 patients, peripheral joint involvement particularly at the lower extremities was observed.

Among the investigated laboratory parameters, the mean ESR of patients was 26.31 ± 20.54 mm/h and the mean serum CRP level was 21.43 ± 19.90 mg/l. ESR and CRP values were significantly higher in the patient group, when compared with the control group ($P < 0.0001$). In the patient group, the mean 25-(OH)D3 level was 21.70 ± 12.17 mmol/l and in the control group, it was found as 32.70 ± 8.77 mmol/l, being significantly lower in the patient group ($P < 0.0001$). No statistically significant difference was found between groups in terms of PTH and bone-specific ALP values ($P > 0.05$). Total calcium and ionized calcium values were significantly lower in the patient group ($P < 0.05$ and $P < 0.01$, respectively). The demographic features and laboratory parameters of the patient and control groups are shown in Table 1.

When the characteristics of medications were investigated, all patients were receiving a nonsteroidal anti-inflammatory drug (NSAID). Ten patients were receiving only NSAIDs, while 68 patients were also receiving sulphasalazine (SSZ), 14 patients were receiving SSZ and methotrexate (MTX), 7 patients were receiving a biological agent, and 1 patient was receiving SSZ together with a biological agent. Twenty-eight patients had a past history of glucocorticoid intake, but for the last 12 months none of the patients had received such a medication.

In BMD measurements with the DEXA method, BMD values of the patient group obtained from lateral lumbar, femur total, neck, and Ward's triangle regions were found to be significantly lower, when compared with the control group ($P < 0.0001$, $P < 0.0001$, $P < 0.01$, and $P < 0.0001$, respectively). No significant difference was noted between anterior–posterior lumbar measurements ($P > 0.05$). Results are shown in Table 2.

Plain radiographies of thoracic and lumbar vertebrae revealed that in the patient group, compression fracture was found in at least one vertebra of the thoracic region in 16% and of the lumbar region in 3%. No fractures were detected in the control group.

Patients with AS were observed by further dividing into two groups as with or without osteoporosis according to lateral lumbar BMD values. A lateral lumbar BMD value of 0.650 g/cm² was taken as the threshold and the patients who had lower values were accepted as osteoporosis (According to Hologic Inc., it corresponds to -2.5 T score for the age group of 30–40 years old). According to this, osteoporosis was found in 32% of patients with AS. In the AS patients with osteoporosis, ESR and CRP values were higher at a statistically significant level, when compared with the patients without osteoporosis ($P < 0.05$). No difference was found between groups in terms of 25-(OH)D3, PTH, and bone-specific ALP ($P > 0.05$), whereas total and ionized calcium levels were significantly lower in patients with osteoporosis ($P < 0.05$, $P < 0.01$). BASDAI scores were higher in patients with osteoporosis, but the difference between groups was not statistically significant ($P > 0.05$). The BASMI scores of patients with osteoporosis were significantly higher ($P < 0.05$). On the other hand, there was no difference between groups in terms of BASFI scores ($P > 0.05$). The results are given in Table 3.

In patients with AS, a negative correlation without statistical significance was noted between the serum 25-(OH)D3 level and ESR, CRP levels determining disease

Table 1 The demographic and laboratory parameters of patients with ankylosing spondylitis and the control group

	Ankylosing spondylitis ($n = 100$)	Control ($n = 58$)	P
Age (year)	39.9 ± 10.9	38.1 ± 9.6	>0.05
Gender (M/F)	75/25	46/12	
Duration of disease (year)	10.50 ± 7.84		
Body mass index (kg/cm ²)	26.05 ± 4.38	25.90 ± 4.50	>0.05
ESR (mm/h)	26.31 ± 20.54	7.53 ± 6.09	$<0.0001^*$
CRP (mg/l)	21.43 ± 19.90	3.57 ± 1.73	$<0.0001^*$
25-(OH)D3 (mmol/l)	21.70 ± 12.17	32.70 ± 8.77	$<0.0001^*$
PTH (pmol/l)	3.95 ± 1.90	3.65 ± 1.27	>0.05
Bone ALP (IU/l)	24.83 ± 12.65	22.96 ± 8.20	>0.05
Total Ca (mg/dl)	9.57 ± 0.38	9.72 ± 0.45	$<0.05^{**}$
Ionized Ca (mg/dl)	4.64 ± 0.25	4.75 ± 0.22	$<0.01^{***}$

ESR erythrocyte sedimentation rate, CRP C-reactive protein, 25-(OH)D3 25-hydroxyvitamin D3, PTH parathormone, bone ALP bone-specific alkaline phosphatase, total Ca total calcium, ionized Ca ionized calcium, *, **, ***: statistically significant

Table 2 The bone mineral density values of the patient and control group

	Ankylosing spondylitis ($n = 100$)	Control ($n = 58$)	P
Anterior–posterior lumbar (g/cm^2)	0.986 ± 0.216	0.987 ± 0.102	>0.05
Lateral lumbar (g/cm^2)	0.737 ± 0.189	0.838 ± 0.111	$<0.0001^*$
Femur neck (g/cm^2)	0.814 ± 0.150	0.890 ± 0.131	$<0.01^{***}$
Femur Ward's (g/cm^2)	0.664 ± 0.194	0.765 ± 0.143	$<0.0001^*$
Femur total (g/cm^2)	0.890 ± 0.144	0.970 ± 0.114	$<0.0001^*$

*, ***, statistically significant

Table 3 Comparison of ankylosing spondylitis patients with and without osteoporosis

	Osteoporosis positive ($n = 32$)	Osteoporosis negative ($n = 68$)	P
ESR (mm/h)	33.09 ± 19.96	23.12 ± 20.17	$<0.05^{**}$
CRP (mg/l)	29.89 ± 25.48	17.45 ± 15.31	$<0.05^{**}$
25-(OH)D3 (mmol/l)	21.17 ± 13.31	21.96 ± 11.69	>0.05
Bone ALP (IU/l)	26.30 ± 12.48	24.13 ± 12.76	>0.05
Total Ca (mg/dl)	9.45 ± 0.41	9.63 ± 0.36	$<0.05^{**}$
Ionized Ca (mg/dl)	4.54 ± 0.29	4.69 ± 0.20	$<0.01^{***}$
PTH (pmol/l)	4.28 ± 2.74	3.79 ± 1.34	>0.05
BASDAI	4.59 ± 1.75	3.94 ± 1.72	>0.05
BASFI	5.38 ± 2.25	4.86 ± 1.97	>0.05
BASMI	5.28 ± 2.45	4.00 ± 2.46	$<0.05^{**}$

ESR erythrocyte sedimentation rate, CRP C-reactive protein, 25-(OH)D3 25-hydroxyvitamin D3, PTH parathormone, bone ALP bone-specific alkaline phosphatase, total Ca total calcium, ionized Ca ionized calcium, BASDAI Bath ankylosing spondylitis disease activity index, BASFI Bath ankylosing spondylitis functional index, BASMI Bath ankylosing spondylitis metrology index, **, ***, statistically significant

activity ($r = -0.181$, and $r = -0.095$, $P > 0.05$, respectively). However, no significant correlation was detected between 25-(OH)D3 and BASDAI scores ($r = 0.011$, $P > 0.05$). In patients, a positive correlation between PTH levels and ESR and a negative correlation without statistical significance between PTH levels, and CRP and BASDAI scores were found ($r = 0.025$, $r = -0.067$, and $r = -0.066$, $P > 0.05$, respectively).

While a negative correlation between duration of disease and bone-specific ALP ($r = -0.228$, $P < 0.05$) was detected, no significant relation with other laboratory parameters was found. There was a negative correlation between duration of disease and femur Ward's triangle BMD values ($r = -0.198$, $P < 0.05$), and there was a positive correlation between anterior–posterior lumbar BMD values ($r = 0.245$, $P < 0.05$). Correlation was found between BASFI ($r = 0.325$, $P < 0.01$) and BASMI ($r = 0.440$, $P < 0.0001$) of Bath indexes and duration of disease. The laboratory parameters that correlated with duration of disease, Bath indexes, and BMD values are given in Table 4.

In terms of BMD measurements, a negative correlation was found only between parameters that are used to evaluate disease activity, namely ESR, CRP, and BASDAI scores and the lateral lumbar BMD values ($r = -0.255$, $P < 0.05$, $r = -0.221$, $P < 0.05$, $r = -0.298$, and

$P < 0.01$, respectively). A negative correlation was found between BASDAI scores and anterior–posterior lumbar, femur neck, and femur total BMD values ($r = -0.242$, $P < 0.05$, $r = -0.201$, $P < 0.05$, $r = -0.241$, and $P < 0.05$, respectively). Except the lateral lumbar measurements, none of the other regions revealed a significant correlation with ESR and CRP values ($P > 0.05$). The results are summarized in Table 5.

Discussion

AS is a chronic, systemic, inflammatory disease with an unknown etiology, it belongs to the spondyloarthropathies group and is related with HLA-B27. Characteristically, it involves the axial skeleton and the entheses regions and in some patients peripheral joints are also affected. AS has several extra-skeletal findings. Among these, eye involvement, cardiac, pulmonary, renal, and neurological involvement, and osteoporosis are important [1].

Bone mineral loss is a common finding in inflammatory rheumatic diseases. With the studies performed in recent years, osteoporosis, which is defined as the disorder of bone tissue microarchitecture and low bone mass, is accepted as a well-known finding of AS. Osteoporosis is

Table 4 The relation between duration of disease and laboratory parameters, Bath indexes, and bone mineral density values

	Duration of disease	
	<i>r</i>	<i>P</i>
ESR	0.020	>0.05
CRP	−0.014	>0.05
25-(OH)D3	0.050	>0.05
PTH	0.008	>0.05
Bone ALP	−0.228	<0.05**
BASDAI	−0.016	>0.05
BASFI	0.325	<0.01***
BASMI	0.440	<0.0001*
Anterior–posterior lumbar	0.245	<0.05**
Lateral lumbar	−0.110	>0.05
Femur neck	−0.117	>0.05
Femur Ward's	−0.198	<0.05**
Femur total	0.027	>0.05

ESR erythrocyte sedimentation rate, CRP C-reactive protein, 25-(OH)D3 25-hydroxyvitamin D3, PTH parathormone, bone ALP bone-specific alkaline phosphatase, BASDAI Bath ankylosing spondylitis disease activity index, BASFI Bath ankylosing spondylitis functional index, BASMI Bath ankylosing spondylitis metrology index, *r* correlation coefficient, *, **, ***: statistically significant

Table 5 The relation between bone mineral density values and disease activity parameters in the patient group

	ESR	CRP	BASDAI
Anterior–posterior lumbar			
<i>r</i>	−0.180	−0.149	−0.242
<i>P</i>	>0.05	>0.05	<0.05**
Lateral lumbar			
<i>r</i>	−0.255	−0.221	−0.298
<i>P</i>	<0.05**	<0.05**	<0.01***
Femur neck			
<i>r</i>	−0.144	−0.130	−0.201
<i>P</i>	>0.05	>0.05	<0.05**
Femur Ward's			
<i>r</i>	−0.110	−0.127	−0.129
<i>P</i>	>0.05	>0.05	>0.05
Femur total			
<i>r</i>	−0.134	−0.192	−0.241
<i>P</i>	>0.05	>0.05	<0.05**

ESR erythrocyte sedimentation rate, CRP C-reactive protein, BASDAI Bath ankylosing spondylitis disease activity index, *r* correlation coefficient, *, **, ***: statistically significant

frequently seen in both the early and the late stages of AS and may cause vertebral fractures [2, 24–27]. The prevalence of osteoporosis in AS is reported between 18.7% and 62% [24, 28]. Studies have shown that axial osteoporosis

prevalence was high even in mild progression and early stages of AS, and it was stated to be responsible from the vertebral fractures in 4–18% of the cases [2, 25, 29, 30]. In this study, osteoporosis was found in 32% of the patients with AS. In the thoracic region of 16% of the patients and in the lumbar region of 3% of the patients, fracture was found in at least one vertebra.

The etiology of bone mineral loss in AS has not been completely clarified and in various studies, it was suggested that different mechanisms such as immobilization caused by pain and spinal restriction, inflammatory cytokines, genetic factors, glucocorticoids used for treatment, and NSAIDs have played a role [3, 4, 31]. It is thought that pain and restriction in the early stage and spinal ankylosing in the late stage cause immobility and thus creates a tendency to osteoporosis [32]. In previous studies, Meirelles et al. reported that in patients with AS, BMD values in the femur regions except the femur neck and in anterior–posterior lumbar regions were significantly lower, when compared with the control group [33]. Franck et al. found that the lumbar BMD values were similar to the control group in both male and female patients with AS, but the BMD values of total hip and femur neck were significantly lower, when compared with the control group [34]. Although negative effects of widely used NSAIDs have not been demonstrated on the bone metabolism in humans, few animal studies have reported that they may cause bone loss [32, 35, 36]. It is a well-known fact that systemic glucocorticoid therapy decreases BMD; however, its use in AS is limited. In this study, although all patients with AS and the control group had been physically active for the last 12 months and had not been receiving glucocorticoid therapy, the BMD values of the lateral lumbar region and femur, measured by the DEXA method were significantly lower in the patient group, when compared with the control group. No significant difference was detected in terms of anterior–posterior lumbar BMD values.

In previous studies, it was found that the decrease in the lumbar and femur neck BMD values detected in early stage of AS became more prominent in cases with slow progression; however, in patients at the late stage, although BMD of the femur neck decreased, the vertebral BMD increased [26, 30, 37]. Studies have reported that there is a relation between the duration of disease and anterior–posterior lumbar BMD values and BMD increases as the duration of disease increases [24, 26, 30, 33, 38]. Today, DEXA is the most preferred densitometry measurement method. In anterior–posterior measurements, besides the vertebral corpus, posterior elements and discs are also involved in the measured area; therefore, both cortical and trabecular bones are evaluated together [39]. Syndesmophytes, ligament calcifications, and fusion of the facet joints, which are characteristics of AS, increase the error

rate in measurements and, particularly in late stage disease, lead to false high BMD values. In this study, it is considered that the positive correlation found between the duration of disease and anterior–posterior lumbar BMD measurement is due to this error. The fact that there is no relation between lateral lumbar BMD measurement and the duration of disease supports this consideration.

Thus, as it was stated before, with the lumbar lateral BMD measurements being superior in detecting the bone loss in the early stage [40, 41], the present authors believe that diagnosis of osteoporosis in either early or late stage AS patients would be more precise, without the need for proximal femur BMD values [32, 33, 42] and treatment could be started.

In recent studies, it was shown that vitamin D is effective not only on calcium, phosphorus, and bone metabolism, but also on the immune system [15, 43]. Amento et al. reported that vitamin D, being an endogenous immunomodulator leading to the suppression of active T cells and cell proliferation, may slow down the inflammatory process [12]. In their study investigating the relation between disease activity in AS and vitamin D, Lange et al. found that high disease activity and disorders in vitamin D metabolism are related with increased bone resorption [5]. In another study, in osteoporotic patients with AS, levels of ESR and CRP were significantly high while vitamin D level was low [4]. It was stated that with the lack of vitamin D, which is an endogenous immunomodulator, proliferation of the T cells and activation cannot be prevented and that the severity of inflammatory process may increase [4]. In this study, vitamin D levels in patients with AS were significantly lower, when compared with the control group. However, no significant relation was found between vitamin D and PTH levels and indicators of disease activity. This finding suggests that in addition to the link between vitamin D and disease activity, vitamin D may also play a role in the etiopathogenesis of this disease.

In their studies, Lange et al. [4] reported that in AS patients with osteoporosis, vitamin D level was significantly lower than AS patients without osteoporosis, whereas ESR and CRP levels were high. In this study, when AS patients with and without osteoporosis were compared, no significant difference was found in terms of vitamin D levels. In patients with osteoporosis, disease activity indicators ESR and CRP were significantly high, while total and ionized calcium levels were significantly low. Moreover, a negative correlation was detected between lateral lumbar BMD values and disease activity indicators ESR, CRP, and BASDAI. In the group with osteoporosis, BASMI scores were also significantly higher. These findings reveal that high disease activity plays a role in the etiology of osteoporosis developed in AS rather than

vitamin D deficiency and that immobilization caused by movement restriction contributes to that process.

As a result, in this study, it was found that the incidence of osteoporosis increases in AS and this might be related with increased inflammatory activity and that vitamin D levels in patients with AS is lower, when compared with the control group. Performing BMD measurements regularly on all patients with AS in the early stage and later is important in order to prevent disability and vertebral fractures that may result in vital complications. Due to its immunomodulatory effects, vitamin D appears to be a hormone that has the potential of playing an important role in the etiopathogenesis of AS and in the control of inflammatory activity. The present authors believe that, in addition to the disease activity indicators, monitoring vitamin D levels would also be useful in order to determine the patients under osteoporosis risk.

Conflict of interest There is no conflict of interest regarding financial or other relationships.

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