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Bone mineral density in women with sarcoidosis

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Abstract Sarcoidosis is a multisystem granulomatous disease of unknown etiology. Almost any organs of the body, but mostly the lungs, are involved. Bone mineral density (BMD) can be affected directly or indirectly in chronic granulomatous systemic diseases such as sarcoidosis. The aim of our study was to evaluate BMD in premenopausal and postmenopausal sarcoidosis patients with or without prednisone treatment and to compare their BMD values with those of a control group having the same menopausal status. Thirty-five premenopausal women (18 untreated, 8 treated, and 9 controls) and 21 postmenopausal women (5 untreated, 5 treated, and 11 controls) were included in the study. All of the patients had a histologically proven diagnosis and were being followed-up at the Sarcoidosis Outpatient Clinic of our unit. BMD of the lumbar (L) spine and femoral neck was measured by dual-energy absorptiometry (DEXA). The subgroups of premenopausals and postmenopausals were compared separately. Comparison among the groups was performed by using analysis of variance. Age, duration of the disease, and body mass index were comparable in treated, untreated, and control subgroups of the pre- and postmenopausal groups, and the subgroups of postmenopausals had comparable durations since menopause. For premenopausals, BMD values at L1–4 were not significantly different among the subgroups ($0.920 \pm 0.08\,g/cm^2$, $0.801 \pm 0.09\,g/cm^2$, and $0.910 \pm 0.05\,g/cm^2$, for untreated, treated, and controls, respectively). However, the BMD value at the femoral neck in treated patients ($0.921 \pm 0.1\,g/cm^2$) was significantly lower than the values in untreated patients ($1.080 \pm 0.2\,g/cm^2$; $P < 0.01$) and in controls ($1.028 \pm 0.17\,g/cm^2$; $P < 0.05$). For postmenopausals, the BMD value at L1–4 in controls ($1.019 \pm 0.07\,g/cm^2$) was significantly higher than the values in untreated patients ($0.783 \pm 0.01\,g/cm^2$) and in treated patients ($0.751 \pm 0.08\,g/cm^2$; $P < 0.001$ for both). The BMD value at the femoral neck in controls ($0.890 \pm 0.1\,g/cm^2$) was higher than the values in untreated patients ($0.745 \pm 0.08\,g/cm^2$) and treated patients ($0.747 \pm 0.1\,g/cm^2$), but the difference was not statistically significant ($P = 0.06$). We concluded that sarcoidosis patients, especially postmenopausal patients with corticosteroid treatment, may have an increased risk of bone mineral loss. Large-scale studies are warranted in order to delineate the exact roles of the disease itself, menopausal status, and corticosteroid treatment in this bone mineral loss.

Key words sarcoidosis · bone mineral density · corticosteroid

Introduction

Sarcoidosis is a multisystem granulomatous disorder of unknown cause [1]. The clinical presentation and natural course of sarcoidosis varies greatly [2]. Although almost any organ of the body can be involved, the lungs or intrathoracic lymph nodes are involved in more than 90% of cases. The incidence of bone involvement in sarcoidosis varies from 1% to 34%, depending on the population the studies are based upon and the radiological criteria used [3–5]. In several reports, different results about osteoporosis were reported [6]. The most common finding about the pathogenesis of bone loss is abnormal calcium metabolism due to the overproduction of dihydrocholecalciferol (1-25$(OH)_2$ D_3) by alveolar macrophages and lymph nodes, and the enhanced activity of bone-resorbing cytokines such as interleukin-1 and tumor necrosis factor, released from osteoclasts surrounding sarcoid granulomas [7].

We aimed to evaluate bone mineral density (BMD) in premenopausal and postmenopausal sarcoidosis patients with or without prednisone treatment and to compare their BMD values with those of a control group having the same menopausal status.

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Patients and methods

Thirty-six female patients who were diagnosed as having sarcoidosis at the Pneumology Department, Cerrahpasa Medical Faculty of Istanbul University, and 20 healthy females were recruited to the study. All 36 patients had histologically proven sarcoidosis. This study was approved by the local Ethics committee, and informed consent was obtained from all subjects. The clinical classification of each patient was made by using the following chest X-ray criteria: stage I, bilateral hilar adenopathy with clear lung zones; stage II, bilateral hilar adenopathy with parenchymal infiltrates; stage III, parenchymal infiltrates without hilar adenopathy. The patients were divided into two main groups according to their menopausal status (pre- and postmenopausal). Each group included subgroups of corticosteroid (prednisone)-treated patients, untreated patients, and controls. The untreated group consisted of 3 patients with stage I, 3 patients with stage II, and 17 patients with stage III. The prednisone-treated group consisted of 1 patient with stage I, 5 patients with stage II, and 7 patients with stage III. The distribution of pre- and postmenopausal women in the treated and untreated groups was comparable. Corticosteroid therapy had been initiated for symptomatic patients and patients with deteriorating lung function. Corticosteroid use was planned as follows: 30 to 40 mg of prednisone daily for 8 to 12 weeks, with gradual tapering of the dose to 10 to 20 mg every other day over a period of 6 to 12 months to establish the minimal effective dose [8]. The mean dose of prednisone given was 19.6 ± 9.2 mg (range, 10–40 mg) for a mean duration of 2.7 ± 1.1 years (range, 1–5 years).

None of our subjects had fractures and none had any other reason for secondary osteoporosis; also, none of our patients had any radiological skeletal findings of osteoporosis. Patients with known causes of bone disease, such as renal failure, thyroid dysfunction, alcoholism, and longterm anticoagulant use were excluded. In particular, the patients had not taken any drugs containing hormones, vitamin D, or other drugs known to affect bone mineral metabolism.

The BMD of the lumbar spine (L1–L4) and femoral neck was measured by dual-energy X-ray absorptiometry (DEXA), using a Hologic QDR 4500 (Hologic, Bedford, MA, USA). Scans were performed and analyzed by the same operator. Calibration was performed weekly with the manufacturer's supplied aluminum spire phantom. The precision error was 1% for the lumbar spine and 2.5% for the femoral neck.

The patients were first evaluated by chest X-ray, complete physical examination, routine laboratory investigations, and study of 24-h urinary calcium excretion. Urinary calcium excretion was studied with the colorimetric test "calcium arsenazo III", using reagents supplied by DiaSys Diagnostics (Holzheim, Germany) [9]. Serum calcium level was measured with an autoanalyzer (model 717; Hitachi, Tokyo, Japan). Subsequently, the patients were referred to the Istanbul University Osteoporosis Research Center for assessing risk factors for osteoporosis, using a standard questionnaire form and measurement of BMD with DEXA.

Values are expressed as means ±SD. The BMD values in sarcoidosis patients with or without treatment and the BMD values in the healthy controls were compared by using analysis of variance. Differences were accepted as statistically significant when $P < 0.05$.

Results

Demographic features of the groups are shown in Table 1. Age, duration of the disease, and body mass index were comparable in treated, untreated, and control subgroups of both the premenopausals and postmenopausals, and the subgroups of postmenopausals had comparable durations since menopause.

For premenopausals, BMD values at L1–4 were not significantly different among the subgroups (0.920 ±

Table 1. Demographic features of the subjects

	Premenopausals			Postmenopausals		
	Untreated group ($n = 18$)	Treated group ($n = 8$)	Control group ($n = 9$)	Untreated group ($n = 5$)	Treated group ($n = 5$)	Control group ($n = 11$)
Mean age (years)[a]	38.2 ± 8.8	41.8 ± 5.4	39.7 ± 7.3	48.2 ± 9.8	49.8 ± 5.4	50.7 ± 7.3
Years since menopause[a]	—	—	—	9.4 ± 4.2	11.2 ± 7.6	12.1 ± 8.1
Duration of the disease (years)	5.65 ± 3.14	5.31 ± 2.39	—	8.68 ± 4.10	9.34 ± 5.34	—
Mean body mass index (kg/m^2)[a]	27.05 ± 4.36	29.62 ± 4.27	28.60 ± 5.24	30.05 ± 2.36	31.02 ± 4.27	28.64 ± 6.23

[a] Mean age, years since menopause, and mean body mass index showed no significant differences among groups

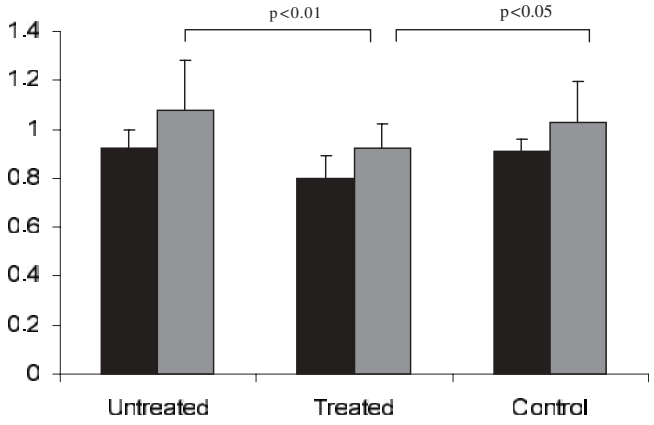

Fig. 1. Mean bone mineral density (BMD) values at lumbar spine (L1–4) and femoral neck in premenopausal women with and without treatment, and controls. *Black and gray columns* denote the results obtained from L1–4 and femoral neck, respectively

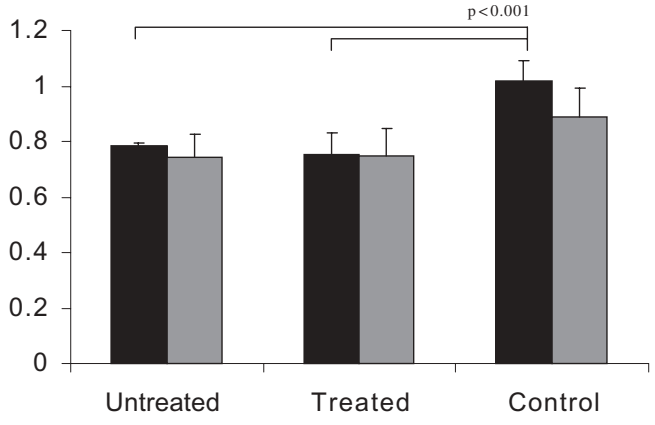

Fig. 2. Mean BMD values at L1–4 and femoral neck in postmenopausal women with and without treatment, and controls. *Black and gray columns* denote the results obtained from L1–4 and femoral neck, respectively

Table 2. BMD values at lumbar spine (L1–4) and femoral neck in pre- and postmenopausal subgroups

	Premenopausals			Postmenopausals		
	Untreated	Treated	Control	Untreated	Treated	Control
BMD value at L1–4 (g/cm^2)	0.920 ± 0.08	0.801 ± 0.09	0.910 ± 0.05	0.783 ± 0.01	0.751 ± 0.08	1.019 ± 0.07***
BMD value at femoral neck (g/cm^2)	1.080 ± 0.2*	0.921 ± 0.1	1.028 ± 0.17**	0.745 ± 0.08	0.747 ± 0.1	0.890 ± 0.1

* Denotes statistical significance when compared with treated premenopausals ($P < 0.01$); ** denotes statistical significance when compared with treated premenopausals ($P < 0.05$); *** denotes statistical significance when compared with untreated and treated premenopausals ($P < 0.001$). The remaining comparisons were not statistically significant
BMD, bone mineral density

0.08 g/cm^2, 0.801 ± 0.09 g/cm^2, and 0.910 ± 0.05 g/cm^2, for untreated, treated, and controls, respectively). However, BMD values at the femoral neck in treated patients (0.921 ± 0.1 g/cm^2) were significantly lower than those in both untreated patients (1.080 ± 0.2 g/cm^2; $P < 0.01$), and in controls (1.028 ± 0.17 g/cm^2; $P < 0.05$) (Fig. 1).

For postmenopausals, BMD values at L1–4 in controls (1.019 ± 0.07 g/cm^2) were significantly higher than those in untreated patients (0.783 ± 0.01 g/cm^2), and in treated patients (0.751 ± 0.08 g/cm^2; $P < 0.001$ for both). The BMD value at the femoral neck in controls (0.890 ± 0.1 g/cm^2) was higher than the values in untreated patients (0.745 ± 0.08 g/cm^2) and treated patients (0.747 ± 0.1 g/cm^2), but the difference was not statistically significant ($P = 0.06$; Table 2 and Fig. 2).

Serum calcium levels and urinary calcium excretion were found to be normal in all subjects.

Discussion

Hypercalcemia (Ca above 11 mg/dl or above 0.11 kg/m^2) occurs in fewer than 10%, and clinically important hypercalcemia occurs in fewer than 5% of patients with sarcoidosis. Hypercalciuria is found more frequently [10]. On the other hand, although abnormalities of bone and calcium metabolism are encountered in a substantial number of patients with sarcoidosis, primary skeletal and bone marrow involvement is rare [10].

There are few clinical studies of BMD in patients with sarcoidosis. The first study, reported by Tervonen et al. [11], demonstrated an abnormally high BMD in patients in the acute phase of sarcoidosis, but in their study, 3 of 21 patients had longstanding disease (for over 2 years). In 1981, Fallon et al. [12] used photon absorption densitometry in patients with sarcoidosis and suggested that bone resorption due to diffuse granulomatosis was an important contributor to the pathogenesis of hypercalciuria and hypercalcemia.

Vergnon et al. [13] reported generalized accelerated trabecular bone loss in ten untreated patients with ac-

tive disease, as proven by bone biopsy. In their study, the histopathology showed that some sarcoid granulomas in bone were surrounded by osteoclasts, and they concluded that sarcoid granulomas have a local osteoclastic stimulating effect.

Glucocorticoid-induced osteoporosis is one of the most serious problems in patients using this drug, and longterm use may be needed for many different reasons [14–16]. In such patients, osteoporosis is very frequent and occurs in up to 70% of the cases [17]. Montemurro et al. [14] demonstrated that bone loss in a longterm prednisone–treated sarcoid population was more frequent than that reported elsewhere in patients with different diseases. In our study, bone loss seemed to be accelerated in the prednisone-treated sarcoidosis population when compared with the untreated patients.

In one report, reversibility of osteoporosis in sarcoidosis patients after prednisone withdrawal was reported [18]. Some investigators have demonstrated that bone mass was significantly decreased in patients with active sarcoidosis, and this was most prominent in postmenopausal females with longstanding disease [17,19]. As the patients for whom glucocorticoid is prescribed have diseases with higher activity, osteoporosis in glucocorticoid users may also reflect this effect.

In a recent study, Hamada et al. [20] have reported that, in women with sarcoidosis, serum calcium and vitamin D levels were inversely correlated with BMD, whereas such a significant correlation was not observed in men with sarcoidosis. In our postmenopausal group, sarcoidosis patients (either treated or untreated) had lower BMD values than the control group, although the difference was not statistically significant for femoral neck values. On the other hand, for premenopausals, treated patients had lower BMD values for lumbar spine than untreated patients or controls, although the difference did not reach statistical significance.

In this study, hypercalcemia and hypercalciuria were not detected in the patients. These patients were followed-up at a specific sarcoidosis outpatient clinic, and their dietary intake of calcium and oxalate was regulated: a low-calcium diet (400 mg/day) and reduced intake of food with a high oxalate content (such as walnuts, hazelnuts, peanuts, almonds, beets, spinach, rhubarb, parsley, chives, chocolate, cocoa, wheat germ, brown rice, tea) were maintained [21].

This restriction of calcium may result in a failure to detect hypercalciuria. The mean duration of the disease in our patients was 5.6 years. Although hypercalcemia has already been reported to be rare, failure to detect hypercalciuria seems interesting.

In sarcoidosis, preventive treatment with calcium or vitamin D is not recommended, and is even contraindicated. Salmon calcitonin and bisphosphonates may be good tools for preventing glucocorticoid-induced osteoporosis [10].

When treatment groups in the same menopausal status is compared, we have found a considerable difference only in femoral neck BMD values of treated and untreated premenopausals. Because the mean age and duration of the disease were different, we did not compare the overall results for pre- and postmenopausals. Nevertheless, in both pre- and postmenopausal patients, the prednisone-treated patients seemed to have lower BMD levels.

There are some limitations in measuring and comparing BMD values in sarcoidosis patients. Untreated patients generally have diseases with much lower activity. Because patients with "active" disease are given treatment, besides steroids, the activity of the disease may be responsible for the result. Due to ethical concerns, it will not be possible to establish a group with active disease but without treatment. On the other hand, the role of menopausal status cannot be evaluated, because postmenopausals accordingly would be of more advanced age and most probably would have disease of longer duration. Probably, failure to compare "matched" groups and conduct a study in a large population may have led to inconclusive results.

In conclusion, sarcoidosis patients, especially the corticosteroid-treated patients, may have an increased risk of bone mineral loss. Preventive therapy for bone loss may be considered in postmenopausal patients receiving longterm glucocorticoid therapy. Large-scale studies are warranted in order to delineate the exact roles of the disease activity, menopausal status, and corticosteroid treatment in this bone mineral loss.

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