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ORIGINAL ARTICLE

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Factors playing a role in the development of decreased bone mineral density in juvenile chronic arthritis

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Abstract *Objective* The aims of this study were to evaluate bone mineral density (BMD) in patients with juvenile chronic arthritis (JCA), compare them with healthy controls, and assess the effects of disease activity and corticosteroid treatment on BMD. *Methods* Twenty-eight patients diagnosed with JCA and 45 healthy controls were included in this study. Disease activity was determined by clinical and laboratory evaluation, Articular Disease Severity Score (ADSS), and the Juvenile Arthritis Functional Assessment Report (JAFAR). Bone mineral density of the lumbar spine was measured by dual energy X-ray absorptiometry (DEXA). *Results* Patients with JCA showed significant decreases in BMD compared with healthy controls. The JCA patients treated with corticosteroids showed significantly lower BMDs than the healthy control group. Age of the patients and age of onset were found to correlate with BMD. *Conclusion* Our study showed that glucocorticoids were involved in the development of osteoporosis in JCA, with many other factors affecting bone mineralization. We could not demonstrate any relationship between BMD and disease activity, but the study data suggest that early onset disease is also an important factor in the development of osteoporosis in JCA.

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Introduction

Osteoporosis is characterized by loss of bone mass and microarchitectural deterioration of the skeleton associated with increased fragility and risk of fractures [1]. As in adult rheumatoid arthritis [2], systemic osteoporosis is also frequently observed in juvenile chronic arthritis (JCA). Recent studies stated that children with JCA have diminished bone mass [3, 4, 5, 6]. As a result, these children have a high risk of diminished linear and skeletal growth [7], osteopenia, and fractures [8, 9].

Besides active arthritis itself, many factors are thought to be possible mechanisms of osteoporosis in children with JCA. These are of a nutritional nature, such as inadequate dietary intake of calcium or vitamin D, low body mass, mechanical factors such as immobility and decreased physical activity, and drugs, especially steroid treatment [1, 10, 13].

Our aims in this study were to evaluate bone mineral density (BMD) in patients with JCA, compare them with healthy controls, and to determine possible causes of osteoporosis in these patients. In other words, we evaluated the relationships between BMD and disease activity, age of onset, duration of disease, daily calcium intake, and corticosteroid treatment.

Materials and methods

Twenty-eight (12 male, 16 female) patients diagnosed with JCA according to European League Against Rheumatism (EULAR) criteria and 45 healthy controls (24 male, 21 female) were included in this study. The mean ages in the patient and control groups were 11.0 ± 4.13 years and 11.13 ± 2.21 years, respectively. Informed consent was obtained from all parents of the patient and control groups. None of the children had a history of other diseases that may effect the bone metabolism. Medical records of the patients were reviewed and, according to steroid use, patients were categorized into steroid and nonsteroid groups. Seventeen

patients (60.7%) had been receiving glucocorticoid therapy for at least 5 months (maximum 33 months), and the minimum required dose was at least 7.5 mg/day of prednisolone (steroid group). Eleven (39.3%) patients had been treated with only nonsteroidal anti-inflammatory drug(s) and formed the nonsteroid group.

After reviewing the patients' medical records, physical examinations were carried out. Types of JCA and duration of disease were noted. Severity of disease was determined by Articular Disease Severity Score (ADSS) [14] and the Juvenile Arthritis Functional Assessment Report (JAFAR) [15]. In addition, laboratory estimates of disease severity included serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. Also, serum levels of albumin, alkaline phosphatase, calcium, and phosphate were measured in the patient group. All the children were on free diets. Dietary calcium intake was documented with a questionnaire, and daily calcium intake was calculated. The BMD values of the patient and control groups were measured by dual-energy X-ray absorptiometry (DEXA) (QDR-4500A Hologic, Waltham, Mass., USA). The skeletal area evaluated was the lumbar region at the level of L1–4.

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) for Windows, version 8.0. Normality of the data was assessed by using the Kolmogorov-Smirnov test, nonnormal distributions were detected, and nonparametric tests were used. The Mann-Whitney rank test was used for comparison of means. The Kruskal-Wallis test was used for group comparisons of BMD values. Spearman's correlation matrix was used to determine the relationships between BMD values, age, age at onset, disease duration time, ESR, CRP values, daily calcium intake, and total steroid dosage. P values lower than 0.05 were accepted as significant.

Results

The clinical and laboratory characteristics of the groups are outlined in Table 1. There was no significant difference between ages of the patient and control groups ($P > 0.05$). The ESR and CRP values were higher in the steroid group than the nonsteroid group, but these differences were not statistically significant ($P > 0.05$).

In the patient group, BMD results were significantly lower than in the control group (0.533 ± 0.14 g/cm^2 in patients and 0.636 ± 0.12 g/cm^2 in controls, $P < 0.01$). The mean BMD results were 0.492 ± 0.15 g/cm^2 in the steroid group, 0.595 ± 0.85 g/cm^2 in nonsteroid group, and 0.636 ± 0.12 g/cm^2 in the control group (Fig. 1). When compared with the control group, the steroid group showed significantly reduced BMD ($P < 0.005$). The nonsteroid group had lower BMDs than the control group, but the difference was nonsignificant ($P > 0.05$).

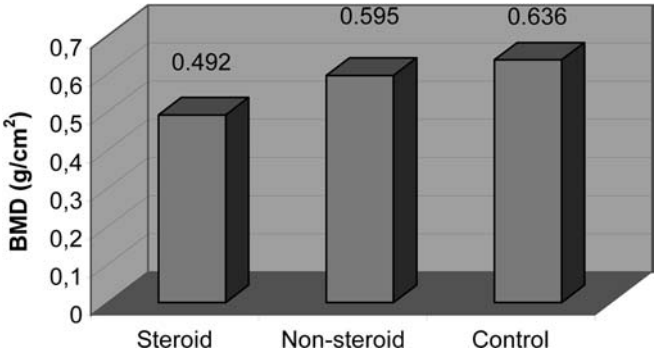

Fig. 1 Bone mineral density of the lumbar vertebrae in the steroid, nonsteroid, and control groups

The mean ADSS and JAFAR scores were 16.58 ± 27.81 and 2.82 ± 7.47 in the steroid group and 20.81 ± 26.27 and 1.72 ± 1.73 in the nonsteroid group, respectively. There were no differences between groups ($P > 0.05$).

There were no correlations between BMD and laboratory markers of disease severity (CRP and ESR), JAFAR, ADSS scores, and total steroid dosage. There were positive correlations only between BMD, age ($P = 0.001$), and age of onset ($P = 0.005$).

Discussion

Generalized osteoporosis and fractures are the major problems in patients with JCA [8, 9]. However, the WHO definition of osteoporosis cannot be applied to children [10] because they have not yet attained their peak bone mass. Certain clinical conditions such as chronic arthritis cause a delay in reaching peak bone mass and result in increased fracture risk. We evaluated the bone mineral status in patients with JCA and demonstrated that BMD was significantly lower than in

Table 1 Characteristics of the patients and healthy subjects. *SD* standard deviation, *BMI* body mass index, *JAFAR* Juvenile Arthritis Functional Assessment Report, *ADSS* Articular Disease Severity Score, *JCA* Juvenile chronic arthritis, *SLE* Systemic lupus erythematosus, *JAS* Juvenile ankylosing spondylitis

Group	Steroid ($n = 17$)	Nonsteroid ($n = 11$)	Control ($n = 45$)
Age in years (mean ± SD)	11.50 ± 4.60	11.22 ± 2.63	11.13 ± 2.21
Males:Females	9:8	3:8	24:21
Oligoarticular JCA	3 (21.4%)	4 (44.4%)	–
Polyarticular JCA	10 (71.4%)	5 (55.6%)	–
Systemic JCA	1 (7.1%)	–	–
SLE	1	–	–
JAS	2	2	–
Disease duration in years (mean ± SD)	5.64 ± 4.68	3.22 ± 3.14	–
Dietary calcium intake in mg/day (mean ± SD)	570 ± 250.75	630 ± 277.98	–
BMI in kg/cm^2 (mean ± SD)	17.09 ± 2.42	17.31 ± 2.89	19.17 ± 3.61
JAFAR (mean ± SD)	2.82 ± 7.47	1.72 ± 1.73	–
ADSS (mean ± SD)	16.58 ± 27.81	20.81 ± 26.27	–

healthy subjects. This finding agrees with other studies in the literature [3, 4, 5, 6, 10, 16, 17]. However, few studies in the literature have concerned the mechanisms of JCA-associated osteopenia, and the results are not consistent. Immobilization or reduced physical activity [3, 10, 11], inadequate dietary intake of calcium or vitamin D [3, 11, 12, 18], and many medications such as glucocorticoids are thought to affect bone mineralization [9, 17, 18, 19, 20]. Glucocorticoids are widely used in the treatment of patients with JCA, and they affect bone mineralization by several mechanisms including suppressing bone formation, increasing bone resorption, reducing intestinal calcium absorption, promoting urinary phosphate and calcium loss, and inhibiting gonadal hormone secretion [21]. However, Henderson et al. reported that patients with JCA who have never received steroid treatment also had reduced BMD [22]. Our study showed that children who received steroid treatment presented lower BMD values than the healthy control group, but in the group that had never received steroids, this difference was statistically nonsignificant. There was no correlation between total steroid dosage and BMD values of the patients in the steroid group. In spite of the limited number of patients, our study showed that glucocorticoids were involved in the development of osteoporosis in JCA, with many other factors affecting bone mineralization.

Many authors have reported that disease activity and duration also play a role in the development of osteoporosis in patients with JCA [3, 12]. We could not find any correlation between BMD values and ESR, CRP, JAFAR, and ADSS. This may be explained by the fact that patients with active disease were under corticosteroid treatment, which suppresses the laboratory and clinical activity parameters. Although BMD was not correlated with duration of disease, it was found to correlate with age of onset. Thus, we concluded that early-onset JCA patients are under increased risk of osteoporosis.

In conclusion, our study demonstrates that in JCA, BMD is adversely affected, especially in the corticosteroid-treated group. Early onset of disease is also an important factor in the development of osteoporosis in JCA. More studies are needed to explain the factors causing decreased BMD in JCA.

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