Sclerotic metaphyseal lines in children and adolescents treated with alendronate

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ABSTRACT

Introduction: Bisphosphonates inhibit bone resorption by interfering with the action of osteoclasts. Among the adverse effects, sclerotic lines observed in the metaphysis of long bones have been described as the main imaging finding in pediatric patients. **Objective**: To evaluate the frequency of radiographic changes caused by alendronate in children and adolescents with low bone density or calcinosis. **Patients and methods:** We conducted a cross-sectional study with 21 patients who were treated with once-weekly alendronate for at least 10 months. Patients underwent x-rays of long bones before the start of alendronate and approximately one year after its use. **Results:** Eleven patients (52.3%) had sclerotic lines in the metaphysis of long bones. The most frequent site was the tibia (8/11 patients), followed by the femur (7/11), humerus (6/11), radius (4/11), ulna (3/11), and fibula (2/11). Regression of radiographic changes during the study period (up to 1.1 years after discontinuation of alendronate) was not observed. **Conclusion:** If used carefully, alendronate is safe and radiographic changes have not been shown to be clinically relevant.

Keywords: alendronate, osteoporosis, calcinosis, sclerotic lines, bone density.

INTRODUCTION

Bisphosphonates are synthetic analogues of pyrophosphate that bind hydroxyapatite and inhibit bone resorption by interfering with the action of osteoclasts.[1] Sodium alendronate is a third generation bisphosphonate.

Its use in pediatric patients is restricted, as its action on skeletal growth has yet to be established and also due to the transplacental effects in an eventual pregnancy.[2] However, some studies have evaluated the efficacy of bisphosphonates in children with osteogenesis imperfecta, idiopathic juvenile osteoporosis, and secondary osteoporosis, especially glucocorticoid (GC)-induced.[3-7] The main indications of bisphosphonates in childhood include: therapeutic failure of the treatment of low bone density for the chronologic age (Z score lower than or equal to -2.0 standard deviations); intolerance to the conventional treatment with calcium and vitamin D; or presence of fractures.[8,9] Its beneficial effects on bone density gain are well known; however, its long-term effects are unknown. Adverse effects, such as abdominal pain, diarrhea, nausea, dyspepsia, esophagitis, and exanthema have been described. Sclerotic lines in the metaphysis of long

Received on 08/17/2009. Approved on 04/28/2010. We declare no conflict of interest.
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bones have been described as the main radiological change in pediatric patients or in patients who have growing plates.[10]

The objective of the present study was to evaluate the frequency of radiological changes caused by alendronate in children and adolescents with low bone density induced by GC or as treatment of calcification of soft tissues (calcinosis).

PATIENTS AND METHODS

A retrospective study was undertaken by obtaining information from the medical records of 21 patients with ages between 8.8 and 22.7 years (mean 16.6 years) from the osteoporosis outpatient clinic of the Pediatric Rheumatology Department of Universidade Federal de São Paulo. Eighteen patients were referred to our service due to low bone mass for their chronological age (Z scores lower than or equal to -2.0 standard deviations). Additionally, three patients used alendronate due to calcinosis associated with juvenile dermatomyositis. All patients were on alendronate weekly for at least 10 months (35 or 70 mg weekly for weights lower or higher than 30 kg, respectively).

METHODS

The bone density of the lumbar spine (L1-L4) was quantified through DXA (Dual-energy X-ray absorptiometry) model DPX, Lunar. The absolute values were converted in scores of standard deviations supplied by the manufacturer.

Patients underwent X-rays of the long bones (humerus, radius, ulna, femur, tibia, and fibula) before beginning alendronate therapy and approximately one year after its use as part of their follow-up routine. The X-rays were analyzed by a radiologist observer (AF), who classified the results as absence or presence of sclerotic metaphyseal lines in the long bones.

RESULTS

Table 1 shows the demographic characteristics of the patients, the age at the diagnosis of low bone density, the time between the diagnosis of low bone density and the onset of alendronate, the period of use of alendronate, the presence or absence of radiological changes, and the location of the sclerotic lines. Patients were on alendronate for low bone density (18 patients) or calcinosis associated with dermatomyositis/polymyositis (three patients). They presented the following diagnoses: bronchial asthma (3), intestinal inflammatory disease (3), juvenile idiopathic arthritis (2), cystic fibrosis (2), idiopathic juvenile osteoporosis (2), allergic rhinitis (1), autoimmune hepatitis (1) osteogenesis imperfecta (1), myasthenia gravis (1), genetic syndrome (1), and muscular dystrophy (1).

Of the patients included in this study, 71.4% were males with age at the time of the evaluation between 9.0 and 22.7 years (mean of 16.6 years), age at onset of low bone density between 5.3 and 17.7 years (mean 12.0 years), and time of evolution of low bone density until onset of alendronate

Table 1
Demographic and clinical data, and radiological changes in patients

Patient	Gender	Age (months)	Age onset osteoporosis (months)	TE osteoporosis until alendronate (months)	Time of use of alendronate (months)	Sclerotic lines	Sites
1	M	224.1	115.5	67.0	18.2	-	—
2	M	249.8	205.1	13.2	12.2	-	—
3	M	237.3	180.5	15.2	21.3	+	Radius and ulna
4	M	265.8	185.7	30.4	12.2	-	—
5	M	127.7	106.4	0.0	12.2	-	—
6	M	241.8	108.8	18.3	26.4	-	—
7	M	272.6	212.7	0.0	36.5	-	—
8	M	136.6	101.0	2.0	20.3	+	Tibia
9	F	238.3	171.3	40.6	11.1	-	—
10	M	178.9	104.8	13.2	12.2	+	Femur and tibia
11	M	272.8	172.4	41.6	17.3	-	—
12	F	146.4	63.2	15.2	10.1	+	Femur, tibia and humerus
13	M	200.5	143.7	32.4	13.2	+	Femur and tibia
14	F	231.5	162.5	21.3	12.2	+	Humeru, radius and ulna
15	M	142.6	*	*	27.4	+	Humerus, radius and ulna
16	F	219.0	175.4	14.2	16.2	-	—
17	F	176.6	139.0	3.1	12.2	+	Femur, tibia, radius and ulna
18	M	162.7	*	*	13.2	-	—
19	M	154.4	*	*	16.2	+	Femur, ulna and humerus
20	M	107.7	81.6	12.2	13.9	+	Femur, tibia, fibula and humerus
21	F	187.2	165.9	8.1	13.2	+	Femur, tibia and fibula

M = male; F = female; TE = Time of evolution.
*Patients with dermatomyositis/polymyositis and calcinosis.

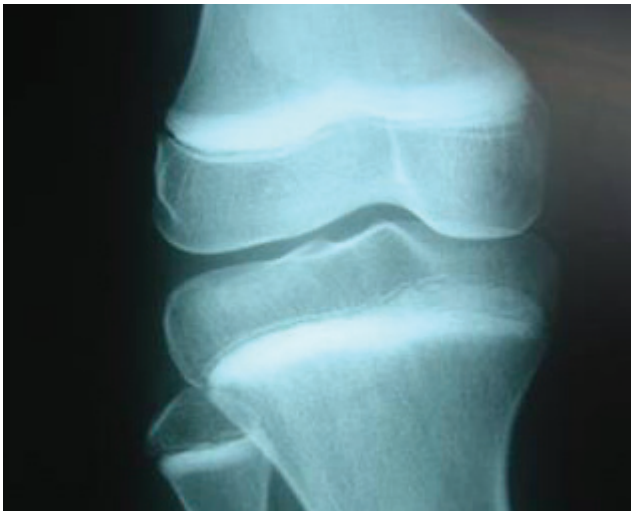

Figure 1
Sclerotic metaphyseal lines in the distal femur, and proximal tibia and fibula.

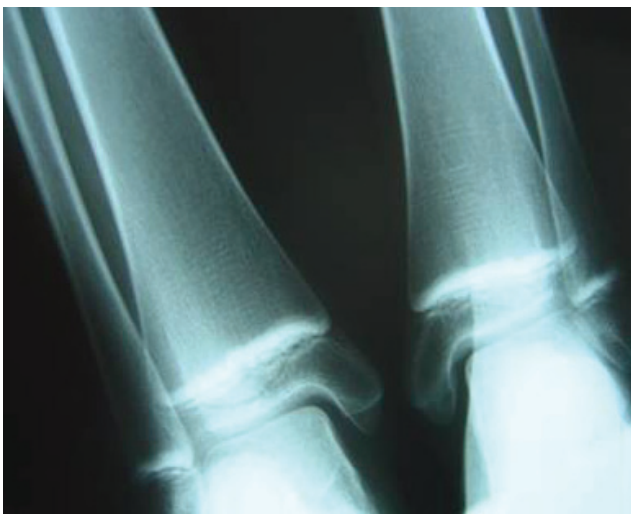

Figure 2
Sclerotic metaphyseal lines in distal tibia and fibula.

between 0.0 and 5.6 years (mean 1.6 years). The duration of alendronate ranged from 0.8 to 3.0 years (mean 1.4 years).

Of the patients evaluated, 11 (52.3%) had sclerotic metaphyseal lines in the long bones (Figures 1 and 2). The most common location was the tibia (8/11), followed by the femur (7/11), humerus (6/11), radius (4/11), ulna (3/11), and fibula (2/11). The growing plates of one girl and four boys of 18 years old, who did not present radiological changes at the time of onset of alendronate, were closed.

Regression of radiographic changes during the evaluation period (up to 1.1 year after alendronate withdrawal) was not observed.

DISCUSSION

Osteoporosis is a public health problem with important social impact and elevated personal and financial costs.[11] Prevention and treatment of low bone mass secondary to rheumatologic diseases in pediatric patients are important to obtain an adequate peak of bone mass, therefore preventing its consequences in menopause and in the elderly.

A consensus regarding the treatment of low bone mass in childhood does not exist. Stimulus for a diet rich in calcium, physical activity and sun exposure, use of calcium and vitamin D, and the effective control of the underlying disease are important.

The use of bisphosphonates in childhood is well established, especially the use of pamidronate, in osteogenesis imperfecta and idiopathic juvenile osteoporosis.[2] Other instances where bisphosphonates have been used in a large number of patients include osteoporosis secondary to the use of GC in patients with systemic diseases and calcinosis.[1,12] Some adverse effects have been reported, such as nausea, vomiting, abdominal pain, esophagitis, uveitis, scleritis, and possible interference in bone remodeling of the growing skeletum.[2] Regarding the linear growth, it has been described that it evolves normally, or even more satisfactorily, during treatment with alendronate.[13] However, its long-term effects are unknown. When these medications are used before closure of the growing plates, sclerotic metaphyseal lines can develop in long bones, without any impact on skeletal growth or maturation.[14] These lines develop at least two months after the onset of the treatment and it is believed that they result from the establishment of a new balance between osteoblastic and osteoclastic activities, *i.e.*, the relative increase in bone formation with high levels of osteoblastic activity close to the growing plates would lead to the development of sclerotic lines.[15] These radiographic findings are reversible after discontinuation of the medication, although it is not known how long it takes them to disappear completely.[16] Their long-term meaning is unknown.

In the present study, patients presented varied causes of low bone mass and, randomly the male gender predominated.

The presence of sclerotic lines was observed in 50% of our patients, which is higher than the results reported in the literature. Studies by other authors are limited to case

reports.[1,2,10,14,16] Unal *et al*. evaluated the efficacy and safety of oral alendronate in 22 patients with osteoporosis (11/22 with connective tissue disease and 13/22 using GC) with ages between 4.3 and 19 years (mean 13.3 ± 3.9 years).[5] The duration of the treatment with alendronate was 14 ± 7.8 months (6 to 36 months). The authors observed sclerotic lines in 63.6% of the patients in knee X-rays (13/22 in metaphysis and 1/22 in epiphysis and metaphysis), especially in pre-pubertal patients.[5] In the present study, the duration of the treatment was 0.8 to 3.0 (mean of 1.4) years. We observed that the presence of sclerotic lines was restricted to those patients with growing plates.

Several authors believe that radiological findings are reversible after the discontinuation of the drug.[1,10,13,16,17] Fernandes *et al*. reported the development of sclerotic lines in two patients (10 and 14 years of age) on alendronate. The authors observed a reduction of sclerotic lines seven months after the discontinuation of the drug, without changes in the patient's growth rhythm.[16] In our population, patients did not show regression of sclerotic lines; however, the time of evolution after the discontinuation of alendronate was 1.1 years. The short evolution time and the fact that these patients were not at the final phase of growth would be an explanation to justify the lack of regression of these changes. Some authors described the regression of radiological findings after closure of the growing plates.[10]

Regarding the location of sclerotic lesions, the tibia was the most often affected, followed by the femur and humerus. Van Persijn *et al*. observed that knees and elbows were the most commonly affected sites.[10] The areas that show faster growth, such as the distal femur, are usually more commonly involved.[1,10,14,16]

Alendronate is indicated in cases the bone mass does not improve, or due to intolerance to conventional therapy with calcium and vitamin D, or in the presence of fractures.[8] The duration of the treatment should not be prolonged, and it should be discontinued as soon as therapeutic response is observed. Although evidence of accumulation of bone microdamage during treatment with bisphosphonates does not exist, this fact should always be considered when this therapy in children and adolescents is planned. If used with criteria, alendronate is safe and, although radiological changes are common in children and adolescents, they are not clinically important.

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