

Pediatric rheumatology

Corticosteroid-induced osteoporosis in children: outcome after two-year follow-up, risk factors, densitometric predictive cut-off values for vertebral fractures

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Abstract

Objectives

To identify factors that contribute to a decreased Z score of volumetric spine bone mineral density (ZvSBMD) and the development of vertebral fractures (VF) in children receiving chronic systemic corticosteroid therapy (SCT); to describe their outcome after 2 years, and to define predictive threshold values for ZvSBMD for VF.

Methods

Fifty-five children on SCT for ≥ 6 months were prospectively followed for 2 years. In children with a ZvSBMD > -1.5 , we prescribed preventive measures for osteoporosis and densitometry annually. In children with ZvSBMD ≤ -1.5 , we prescribed spine x-rays and those with VF received alendronate. The association between clinical and biochemical variables and the presence of VF or ZvSBMD were analyzed by logistic regression or multiple regression analysis. The threshold value of ZvSBMD for predicting VF was determined by ROC curve and the probability of having a VF was modeled by multiple logistic regressions.

Results

Children who do not develop osteoporosis at first evaluation tend to maintain normal ZvSBMD after two years. Alendronate increased ZvSBMD (median: at baseline: -2.69 ; 1 yr: -1.92 ; 2 years: -1.39 , $p < 0.001$). The threshold value of ZvSBMD for predicting VF was -1.8 . In this cohort, the risk of developing VF was significantly higher in children who were not ambulatory, growth retarded, treated with methotrexate for a longer time, had a family history of osteoporosis or were of non-aboriginal ancestry.

Conclusion

Children on SCT, who do not develop osteoporosis, tend to maintain normal BMD. Children who were not ambulatory, on methotrexate or growth retarded have higher rates of VF.

Key words

Corticosteroid-induced osteoporosis, methotrexate, growth retardation, physical activity, vertebral fractures, children.

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Introduction

The most important secondary cause of osteoporosis in children is chronic exposure to glucocorticosteroids, which are used for an extraordinarily large number of disorders (1). The underlying diseases are usually severe, and corticosteroid-induced-osteoporosis (CIO) is a complication that may impair the quality of life of these children (2, 3). Considerable variation exists in the susceptibility of developing osteoporosis during systemic corticosteroid therapy. Despite important advances in CIO in adults, little information exists about risk factors and prognosis of CIO in children (4). The aims of this study were: 1) to identify factors that contribute to decreased volumetric spine bone mineral density (vSBMD) and the development of vertebral fractures in children receiving chronic corticosteroid therapy; 2) to define predictive threshold values for vSBMD for vertebral fractures; and 3) to describe the outcome of these children after 2 years of follow-up.

Material and methods

Study design

Prospectively, patients receiving oral or intravenous corticosteroid therapy for more than 6 months were followed-up from 4 pediatric centers in Chile. All patients were followed at the Bone Metabolic Unit, Pediatrics Department, Pontificia Universidad Católica de Chile. In patients with a Z score of vSBMD (ZvSBMD) ≤ -1.5 , spine x-rays were performed. Patients with a ZvSBMD > -1.5 were followed-up with a BMD every year while on corticosteroids. Since the first visit, all patients were shown conventional preventive measures including the adjustment of diet to the normal requirements for age (particularly calcium and protein intake), the increase of weight-bearing physical activity, the use of standing frames for 10 minutes, 3 times a day (when the patient was unable to stand up), and for assuring normal vitamin D status, prescribing a supplement to keep 25 dihydroxy vitamin D levels between 50-100 nmol/L (20-40 ng/mL). A diagram of the study protocol is shown in Figure 1.

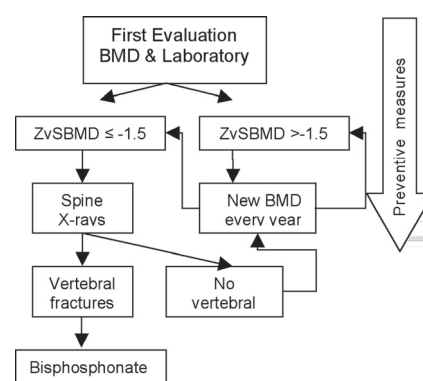


Fig 1. Protocol schedule. BMD: Bone mineral density; ZSBMD: Z score of volumetric spine bone mineral density.

Evaluation

1. Clinical and demographic information: We recorded information about ethnicity, type and time of duration of the underlying disease, time spent on corticosteroids, type and doses of corticosteroids, dose of and time on methotrexate, hydroxychloroquine, or cyclophosphamide, and the family history of osteoporosis. Aboriginal ancestry was considered positive when one of the parents had an aboriginal family name. The family history of osteoporosis was recorded as positive when at least one first or second degree relative had osteoporosis. The doses of corticosteroids were standardized according to the potency of prednisone. The dosage of corticosteroid at baseline was defined as the median daily dose per kg received from the start of this therapy to the time of the first densitometry, at the first year as the median dose received from the first to the second densitometry, and at the second year as the median dose from the second to the third densitometry. Underlying diseases were defined by criteria published elsewhere (5-9). In addition, we reviewed growth records, calcium intake, and degree of physical activity. The daily average calcium intake was estimated from a one-week recall diet. A normal calcium intake was considered 1000 mg/day for prepubescent and 1500 mg/day for pubescent children. The degree of physical activity was arbitrarily divided into 2 levels: 1) no walking or walking rarely and 2) walking on regular basis.

2. Anthropometry: The standing height

was measured with a stadiometer (Holtain Ltd., Crymch, Dyfed, U.K.). The patient's weight was measured with a balance-beam scale (Seca™). Both weights and heights were converted to Z scores to adjust for chronological age and sex, using the National Center for Health Statistics (NCHS) growth reference, calculated by software Epi-Info 2000, version 6.0 (www.cdc.org), which has been shown to be applicable to the Chilean population (10). Growth retardation was defined as a growth velocity < 5th percentile for age and sex during a period of observation greater than 8 months.

3. Densitometry: All assessments were performed at the Radiology Department of the Pontificia Universidad Católica de Chile, with the same densitometer throughout the study. BMD of the lumbar spine (L2-L4) was measured in both the normal and study group children by dual x-ray absorptiometry (DXA) using a Lunar densitometer, pediatric software version 4.7d (Lunar DPX-L, Lunar Radiation Corp., Madison, WI) with a precision of 1-2%. Because of the frequent association of corticosteroid therapy with short stature, we used volumetric BMD, rather than areal BMD. The volumetric BMD from L2-L4 was calculated, as reported by Kröger *et al.*, with the formula: Volumetric BMD = BMC/Volume = BMD * [4/(π * Width)] (11). The validity of this model was assessed using *in vivo* volumetric data obtained from magnetic resonance imaging of lumbar vertebrae (12). In children who have a fractured lumbar vertebral body, Z score values of volumetric BMD (ZvSBMD) were recalculated using non-fractured bodies. ZvSBMD were calculated using reference values from Chilean children. This reference population was constituted by children of both sexes, 2 to 18 years old (n = 14-18 for each year interval). The eligibility criteria for the reference population was as follows: healthy, birth weight > 2500 g, adequate calcium intake, height $\pm$ 2 SD, BMI between p25-75 (NCHS); normal onset of puberty, regular menses 2.5 years post-menarche, physical activity between 2 to 6 hr/week. The exclusion criteria were as follows: any chronic

medications, history of fractures, family history of early osteoporosis, other bone diseases or urinary stones. All children had a physical examination including determination of the Tanner stage (13).

4. Laboratory: In each patient, serum levels of calcium, phosphate, total alkaline phosphatases, parathormone, creatinine, total proteins, albumin, alanine aminotransferase, aspartate aminotransferase, urine calcium/creatinine and urine D-Pirilinx/creatinine ratios were measured [methods reported previously (14)]. Additionally, serum 25 (OH) vitamin D was measured (15).

5. Evaluation of vertebral fractures: In patients with a ZvSBMD $\leq$ 1.5, spine x-rays were performed. The parameters used to define vertebral fracture were: a difference between the anterior and posterior height of the vertebra higher than 20%, wedge; or symmetrical crushing: fish vertebra or a difference in anterior and posterior height, greater than 20% relative to adjacent vertebrae.

6. Intervention: Children diagnosed with vertebral fractures were enrolled in an open label protocol of bisphosphonates. Children with a weight < 30 kg received 35 mg of alendronate once a week, and children with a weight $\geq$ 30 kg received 70 mg once a week. Conventional preventive measures were continued during alendronate treatment. An 8-year-old boy with juvenile idiopathic arthritis, suffering from gastritis, received pamidronate 1.5 mg/kg/cycle every 6 months. Bisphosphonate therapy was stopped when ZvSBMD reach a value close to zero. This protocol was approved by the Ethics Committee of the Faculty of Medicine at the Pontificia Universidad Católica de Chile and informed consent was obtained from the parents or guardians of the enrolled children.

Statistics

Values were expressed as medians and ranges in parentheses, or otherwise stated. Data on the first evaluation were analyzed by the Mann Whitney test, and later, by the Fisher Exact test to separate the variables when the variables were continued. Data on the fol-

low-up were analyzed by Friedman's test. Associations between ZvSBMD and the presence of fractures and clinical and biochemical variables were analyzed by stepwise multiple regression or stepwise logistic regression analysis, respectively. The threshold value (best point of coincidence between sensitivity and specificity) of ZvSBMD for predicting vertebral fractures was determined by the receiving operating characteristic (ROC) curve, and the probability of having a vertebral fracture was modeled by logistic regressions. A p value <0.05 was considered significant. Statistical analyses were carried out using SPSS 13.0 (SPSS, Chicago, IL).

Results

Fifty-five children were evaluated, 37 of whom were female, aged 11.1 (2.2-15.3) years old. The underlying diseases were: juvenile idiopathic arthritis in 13 of the patients; systemic lupus erythematosus in 9 of the patients; dermatomyositis in 7 of the patients; nephropathies in 5 of the patients; bowel inflammatory diseases in 5 of the patients; hematological disease in 4 of the patients (autoimmune anemia in 3 and Fanconi anemia in 1); chronic graft-versus-host disease in 2 of the patients (cardiac transplant in 1; bone marrow transplant in 1); mixed connective tissue disease in 2 of the patients; undifferentiated connective tissue disease in 3 of the patients; primary angiitis of the central nervous system in one patient; chronic uveitis in 3 of the patients; microscopic polyarteritis in one patient.

The duration of the underlying disease was 2.3 (0.1 - 13.3) years. The type of corticosteroid was prednisone in 48 of the patients; deflazacort in 3 patients and metilprednisolone in 4 patients with a median daily dose of 1.0 (0.5-10.0) mg/kg. Time on corticosteroids at baseline was 1.9 (0.1 - 13.3) years. Twenty-two children were given methotrexate; time on methotrexate at baseline was 1.37 (0.5-7.92) years; and the weekly dose of methotrexate was 11.45 (9.4-16.6) mg/mt². Nine children received hydroxychloroquine, and three children received cyclophosphamide. Median calcium intake was 1000.0

(200.0- 2000.0) mg/day, but 22 children had a calcium intake under recommendation. Physical activity: walking in 40 children (72.7%); no walking in 15 children (27.3%). The mean (SD) height Z score was -1.78 (0.78) and the mean (SD) body mass index Z score was +2.54 (1.21). None of these children received growth hormone therapy during this study. Growth retardation was diagnosed in 25 children (45.5%). Family history of osteoporosis was present in 7 children (12.7%), 6 children had a grandmother with postmenopausal osteoporosis and one had a mother with osteoporosis. The median Z score vSBMD was -0.91 (-9.2 - 1.9); only in 9 patients (16.4%) was the Z score $\leq$ -2.0. Nineteen children had vertebral fractures, 7 (36.8%) of these children were symptomatic, reporting a significant back pain. Fourteen patients had only thoracic vertebral fractures; five patients had both thoracic and lumbar vertebral fractures. Nevertheless, all of them have at least two non-fractured lumbar bodies. 17 patients had 1 to 3 fractured vertebral bodies, two patients had 4 to 5 fractured vertebral bodies, and no patients had more than 5 vertebral fractures. Clinical and laboratory characteristics of fractures versus non-fractures in children and the results of the univariate logistic regression are shown in Table I.

Stepwise logistic regression showed that presence of vertebral fractures was associated independently to a lower ZvSBMD (Odds ratio = 0.448; $p = 0.001$), less physical activity (Odds ratio = 0.086; $p = 0.043$), more growth retardation (Odds ratio = 10.11; $p = 0.046$), and more time on methotrexate (Odds ratio = 3.42; $P = 0.037$). We found that a lower ZvSBMD was independently associated with: presence growth retardation ($\beta = -1.82$; $p = 0.04$), longer period on methotrexate ($\beta = -3.34$; $p = 0.001$) and less degree of physical activity ($\beta = -3.42$; $p = 0.001$). There was no significant association between ZvSBMD and presence of vertebral fracture and type or time of duration of underlying disease, time on corticosteroids, type or doses of corticosteroids.

Thirty-one children out of 36 (81.1%)

Table I.

Clinical characteristics	Vertebral fracture present		p value
	No (n = 36)	Yes (n = 19)	
Age (years)	10.4 (2.8 - 15.3)	11.3 (2.2 - 15.3)	0.818
Sex (female/male)	22/14	15/4	0.234
Time of duration of disease	2.2 (0.1 - 13.3)	2.3 (0.4 - 8.9)	0.466
Dose of corticosteroid (mg/kg/day)	1.0 (0.5 - 3.5)	1.0 (1.0 - 10.0)	0.236
Time on corticosteroid (years)	1.4 (0.1 - 13.3)	2.3 (0.4 - 8.9)	0.129
Use of methotrexate	12	12	0.047
Time on methotrexate (years)	0.0 (0.0 - 7.0)	0.9 (0.0 - 7.9)	0.037
Calcium intake (mg/day)	812.0 (200 - 2000)	1050.0 (200 - 1820)	0.318
Growth retardation present	9	16	<0.001
No walking/ walking	3/33	12/5	<0.001
25 OH vitamin D (nmol/L)	40.9 (24.9 - 87.1)	32.2 (12.5 - 68.1)	0.069
Parathyroid hormone (pg/mL)	39.0 (11.8 - 111.0)	43.0 (5.4 - 84.3)	0.234
Alkaline phosphatases (UI/L)	204.5 (76.0 - 648.0)	165.5 (20.6 - 394.0)	0.315
Family history of osteoporosis	2	5	0.041
Aboriginal ancestry	5	1	0.035
Z Spine volumetric BMD	-0.2 (-1.7 - 1.9)	-2.3 (-9.2 , -1.0)	<0.001
Urinary calcium/creatinine ratio (mg/mg)	0.06 (0.01 - 0.5)	0.07 (0.01 - 0.6)	0.804
Urine D-pirilix/creatinine ratio (nmol/nmol)	36.3 (24.2 - 50.8)	38.4 (22.6 - 45.8)	0.203

without vertebral fractures completed follow-up for two years. The median daily dose of corticosteroid for non-fractured children by the end of the first year was 0.80 (0.5-2) mg/kg, and by

the end of second year was 0.75 (0.4-2) mg/kg. ZvSBMD in these children did not change significantly in this period (Fig. 2A). The median daily dose of corticosteroid for nineteen fractured

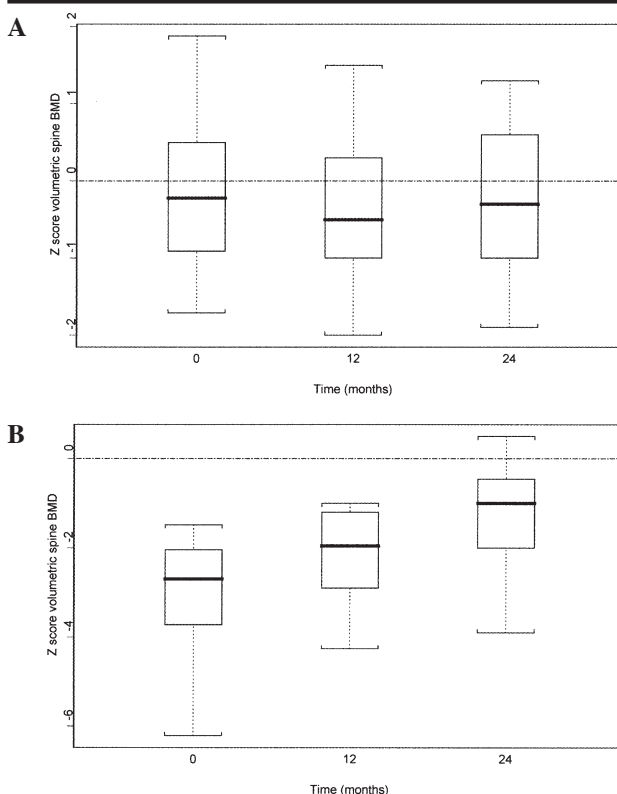


Fig 2. Z score of volumetric bone mineral density on follow-up; A: in 31 children without vertebral fractures; B: in 19 children with vertebral fractures treated with bisphosphonates. The box plots spread from the 25th to 75th percentiles (lower and upper quartile respectively), central bold line represent median, and the difference of the ends of the whiskers is the range (if there are no outliers).

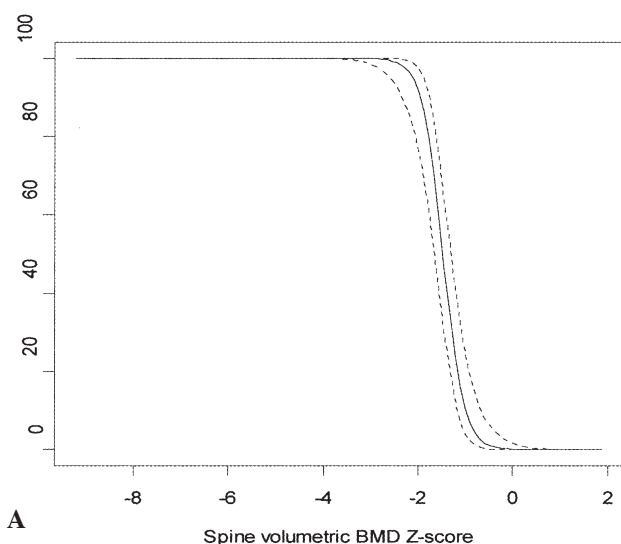
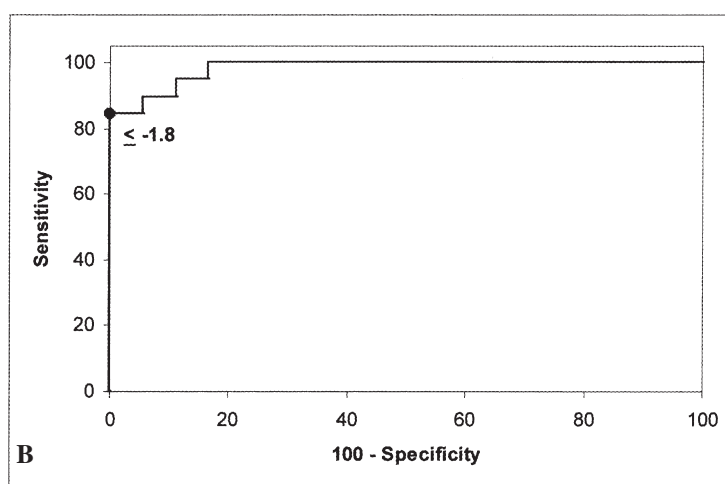


Fig 3. A. Probability of having a vertebral fracture versus Z score of volumetric bone mineral density. Solid line represents mean and pointed lines 95 confident limits. **B.** ROC curve, points represent the value of ZSBMD of best coincidence between sensitivity (84.2%) and specificity (100%). The area under the curve was 0.982, confident limits 95% 0.903 - 0.997.



children by the end of the first year was 1.0 (0.5-2) mg/kg, and by the end of second year was 0.8 (0.4-2) mg/kg. All these children received bisphosphonates and increased significantly ZvSBMD, from a median of -2.69 to -1.92 at the end of first year, and -1.39 at the end of the second year ($p < 0.001$) (Fig. 2B). The median time on bisphosphonates was 2 (1.6-2) years. In children treated with bisphosphonates, urine D-Pirilnx/Creatinine ratios decreased in 35 (12-52) % after 3 months of initiated therapy and tended to stay reduced along the two years of bisphosphonates therapy. Additionally, 12 out of 19 children showed an increase in height of vertebral bodies on x-rays after one year.

The probability of having a vertebral fracture increased dramatically with ZvSBMD values less than -2.0 (Fig 3A). The threshold value of ZvSBMD

for predicting vertebral fractures was -1.8 with a sensitivity of 84.2% and specificity of 100%. The area under the curve was 0.892, confident intervals 0.903 - 0.997 (Fig. 3B).

Discussion

We report outcomes of children on chronic corticosteroid therapy after two years follow-up, factors associated to CIO and the predictive threshold value for vertebral fractures. Of note, this study was constituted of children with particularly severe diseases, who usually need corticosteroid in high dose and for prolonged periods of time.

We found a strong correlation between the presence of growth retardation and vertebral fractures, as well as decreases of ZvSBMD, as also reported by Kotaniemi *et al.* (16, 17). A confounding factor may be present in this association, since a reduction in height could

be due to the presence of vertebral fractures. However, in these patients, the reduction in growth velocity was observed immediately after corticosteroid was started, while vertebral fractures were detected after 6 months. Moreover, most of our patients presented 1 to 3 fractured vertebrae, which estimates a decrease in height less than the height deficit observed after the 8 months of follow-up that we demanded to define growth retardation. This association could be explained by the decrease of growth factors that modulate both mineral accretion and growth. Corticosteroid effects on the growth hormone axis have been extensively studied, demonstrating inhibition of growth hormone secretion, somatomedin production and transforming growth factor receptor expression (18-21). Clinical trials of growth hormone in children on corticosteroid therapy have shown an increase in height and BMD in these children, findings which emphasize the interdependence between growth and bone mass (22-27).

To our knowledge, only one study has addressed the effect of methotrexate on bone in children with similar doses than reported in this cohort. In this study, Bianchi *et al.* failed to find a correlation between the use of methotrexate and BMD in children with juvenile rheumatoid arthritis (28). In the present work, we found that in children on systemic corticosteroid, methotrexate, independent of other factors, further contributed to diminished BMD and more importantly, contributed to increased risk of vertebral fracture. This contrast could be due to the small number of patients on methotrexate and corticosteroids in the study of Bianchi (16 children). In addition, the tight range of corticosteroid dose in our subjects may make the deleterious effect of methotrexate on BMD and fracture risk evident. Another possible explanation is a synergistic negative effect of methotrexate and corticosteroids when used together.

Few studies have addressed the relationship between doses of corticosteroids and decreases of BMD in children. Mul and el-Husseini were able to find a significant negative correlation be-

tween the doses of corticosteroids and ZvSBMD (28, 29), but Castro *et al.* did not (30). In the present study, we could not find such a correlation. However, the doses of corticosteroids in these children were quite homogeneous, so it may be statistically difficult to detect an association.

In addition to previous studies (31, 32), we have found a significant association between physical activity and ZvSBMD and the risk of vertebral fracture. This association was very strong, and ZvSBMD appears to decrease mainly when a child is not able to walk on a regular basis. This observation agrees with the finding that muscle force appears to be the main determinant of bone mass in different reports (33-36). Unexpectedly, we could not demonstrate an association between calcium intake and vitamin D status and low BMD, despite having a considerable proportion of children in the study who were under the nutritional recommendations. This finding might be explained by the ethnic differences found in the metabolic impact of low levels of 25 dihydroxyvitamin D. It has been reported that Chinese adolescents affected by hypovitaminosis D have a significantly higher absorption and lower urinary excretion of Calcium compared with American adolescents, which represents a greater ability to optimize calcium retention (37). In a group of Argentine children with vitamin D deficit, Olivieri *et al.* also failed to find a reduction of BMD (38). Also, corticosteroids could decrease calcium absorption, reducing the effect of calcium intake on BMD (39).

Interestingly, we found that children with a family history of osteoporosis were more predisposed to have a vertebral fracture than those that did not. At the same time, we found that aboriginal ancestry in these children appears to be a protective factor to develop vertebral fracture while on corticosteroid therapy. This finding suggests a strong role of genetic variables on BMD and bone fragility (40). These two observations open interesting opportunities for investigation on the field of genetics and corticosteroid-induced osteoporosis, as proposed by Mazziotti *et al.* (41).

Comparable to the experience in adults, this study showed that children develop osteoporosis early after initiation of corticosteroid therapy (41). Remarkably, after two years, most children who had a normal BMD at first evaluation will not develop osteoporosis, despite continuing systemic corticosteroid therapy. This could be due to an improvement of the underlying disease, reduction of corticosteroid doses, protective genetic factors, or prescription of preventive measures. Even though we consider it unethical to test the last hypothesis, we feel that preventive measures, particularly encouraging of weight-bearing exercises, could change the natural course of CIO in children. So far, this is the first study reporting longitudinal outcomes of children on corticosteroids at two years.

Even though, we could not find a significant association between ZvSBMD or the presence of fractures and type of disease, duration of disease; it is difficult to separate the use of methotrexate, growth retardation and physical activity from other possible factors related to the severity of underlying disease itself, particularly inflammatory activity.

Factors associated with a lower spine BMD and vertebral fractures identified in this study may be useful to plan specific follow-up protocols, and preventive strategies, thus focusing to a higher risk group to design intervention studies. Also, they open interesting opportunities to further research on the pathogenesis of CIO in children.

One of the strengths of this study is to have vertebral fractures as an outcome enclosed in the analysis and conclusions, considering the open controversy about BMD and its interpretation in children, especially when they are affected with short stature (42, 43).

Despite the wide use of BMD to evaluate children at risk of osteoporosis, there is no reported information about Z score BMD values and risk for vertebral fractures. By logistic regression and ROC curve we determined a risk threshold value for ZvSBMD of -1.8. Thirty-seven percent of these fractures were symptomatic, a percentage similar to that reported in adults on corticosteroids (41). Hence in about 62% of the

patients, fractures could have presented some time before the densitometry. Determination of predictive cut-off values and risk assessment could be useful when conducting intervention trials, and especially to decide how much to increase BMD with therapeutic measures in order to significantly reduce the risk of osteoporotic fractures. This is the first study proposing threshold level for predicting vertebral fractures in children exposed to high doses of systemic corticosteroids.

In this open labeled protocol of administration of bisphosphonates in children with vertebral fractures, we saw a significant improvement of BMD compared with baseline along the two years observation period. Moreover, we detected remodeling with an increase of height of vertebral bodies in most of treated children. Nevertheless, this is not a controlled trial, so, more explanations are possible for these positive results. Recently, Bianchi and Rudge have reported controlled trial of use of alendronate in children with juvenile idiopathic arthritis, showing a significant increase of spine BMD in children treated compared with controls (44, 45). In adults, preventive therapy with bisphosphonates has been proposed (46, 47). While long-term side effects of bisphosphonates in children are not elucidated, their preventive use is not recommended.

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