Prevalence of Vertebral Fractures in Children with Chronic Rheumatic Diseases at Risk for Osteopenia

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Objectives To determine the prevalence of and the risk factors for vertebral fractures in a cohort of children with chronic rheumatic diseases considered at risk for osteopenia.

Study design We conducted a cross-sectional study of patients with chronic rheumatic diseases at the Montreal Children's Hospital.

Results Of the 90 study participants (22 boys, 68 girls), 10 boys and 7 girls (19%) were found to have vertebral fractures. These 17 children had a total of 50 fractures, an average of 2.9 per affected child. Fractures in the upper thoracic region (T5-8) accounted for 55%. Only 56% of all fractures were symptomatic. With multivariate regression, we identified male sex ($P < .01$), body mass index z-score ($P < .02$), and cumulative glucocorticoid dose ($P < .01$) as significant predictors of the number of vertebral fractures.

Conclusions Our study examined the prevalence of vertebral fractures in a high-risk pediatric population. Nineteen percent of our cohort had vertebral fractures. Significant risk factors for the development of vertebral fractures include male sex and cumulative glucocorticoid dose. Better understanding of the extent of the problem in this population will allow us to further refine screening guidelines and treatment in these patients. *(J Pediatr 2009;154:438-43)*

Osteoporosis is a skeletal disorder characterized by low bone mass and deterioration of bone microarchitecture, resulting in fragility fracture susceptibility. In children, low bone mass is caused by poor bone accrual and ongoing bone loss caused by a number of factors. These include inadequate calcium and vitamin D intake, chronic illness, limited weight-bearing activity, medications, and hormonal imbalances. In adults, age-related fractures associated with osteoporosis are a well-known entity, contributing to significant morbidity.[1] In children with chronic illnesses, osteoporosis, fragility fractures, and bone pain have increasingly been recognized as a source of morbidity.[2-4] However, the extent of this problem is poorly understood. Studies examining vertebral fractures in children have been limited to case reports or have restricted their study population to children treated with glucocorticoids or with low bone mineral density (BMD).[4,5] Other studies have relied on an indirect method of vertebral fracture identification by using dual-energy x-ray absorptiometry (DXA) targeting scans, which have subsequently been invalidated by the authors themselves.[3-7] A global assessment of children at risk of vertebral fractures is still lacking. Moreover, issues such as prevalence, risk factors, and natural history of vertebral fractures in children remain largely unknown.

The rheumatology population is at particular risk for osteoporosis and fragility fractures because of the chronic inflammatory nature of the disease,[8-10] the medications used to control disease activity, including glucocorticoids and methotrexate,[11-13] and the associated reduced physical activity and delayed puberty,[14] which independently contribute to fracture risk. We sought to determine the prevalence and predictors of vertebral fractures in this at-risk population by using plain thoracic and lumbar spine radiographs,

BMC	Bone mineral content	JDM	Juvenile dermatomyositis
BMD	Bone mineral density	JIA	Juvenile idiopathic arthritis
BMI	Body mass index	SLE	Systemic lupus erythematosus
CTD	Connective tissue disease	vBMD	Volumetric BMD
DXA	Dual-energy x-ray absorptiometry		

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which remain the radiographic gold standard.[15] We also set out to determine the predictors of low BMD.

METHODS

In April 2005, we reviewed the charts of all patients observed in the rheumatology clinic at the Montreal Children's Hospital and identified 113 individuals who met our inclusion criteria. From April 2005 to December 2006, we invited these children and adolescents who fulfilled criteria for being at risk for osteopenia and who were observed in the rheumatology clinic at Montreal Children's Hospital to participate in the study. Children as old as 18 years were included when they had earlier or current exposure to methotrexate, corticosteroids, or both and had the following diagnosis: juvenile idiopathic arthritis (JIA; either polyarthritis, systemic arthritis, extended oligoarthritis, or psoriatic arthritis with ≥5 affected joints); connective tissue disease (CTD), including systemic lupus erythematosus (SLE) and juvenile dermatomyositis (JDM); and systemic vasculitis. Children with preexisting conditions that could affect calcium homeostasis were excluded, including those with hyperthyroidism, parathyroid disorders, malignancy, or primary bone disease. Parental informed consent and patient's assent were obtained. Study participants and subjects who refused to participate were compared for age at diagnosis, duration of disease, and diagnosis.

We reviewed the charts of the study subjects and extracted these characteristics: age at diagnosis, age and duration of disease at time of enrollment, associated diagnoses, and other medical problems. Total lifetime exposure to oral and intravenous glucocorticoids was recorded. We converted the glucocorticoid dosage to prednisone equivalency and also expressed this as prednisone per kg of body weight. Also, we recorded the lifetime cumulative methotrexate doses in the form of mg per m^2 of body surface area.

At the time of enrollment, a standardized food frequency questionnaire was administered to patients and their parents, from which daily calcium (mg) and vitamin D (IU) intakes were calculated.[16] In addition, patients and parents were asked to complete a questionnaire about their personal and family history of fractures, osteoporosis, age of pubertal onset, and use of medications or supplements. At the same clinic visit, children were examined and Tanner staging was performed on all study subjects. Heights and weights were measured with a standard hospital scale and a Harpendon stadiometer. The heights were measured in triplicate, and the average was calculated. Heights and weights were converted to z-scores by using the Centers for Disease Control and Prevention-National Center for Health Statistics 2000 protocol.[17]

All patients enrolled underwent plain lateral thoracic and lumbar spine radiography. These radiographs were read by 1 of 2 trained radiologists (E.M.A. or N.S.), experts in reading pediatric vertebral fractures, who were blinded to the underlying diagnosis in the patients. The senior author reviewed all films. When there was a discrepancy, the films were re-read by the second pediatric radiologist. Vertebral fractures were graded on the basis of the semi-quantitative scoring method of Genant.[15] The Genant scoring system assigns a score for each vertebra from T4 to L4 (Figure). Grade 0 corresponds to a normal vertebral body, grade 1 to a mild fracture (20%-25% reduction in anterior, middle, and/or posterior height), grade 2 to a moderate fracture (26%-40% reduction in height), and grade 3 to a severe fracture (>40% reduction in height). A grading of 0.5 was used for minimal changes of the vertebral height or shape that did not fulfill criteria for Genant grade 1 and were considered normal variants. A Genant score ≥1 was considered to be a definite compression fracture of the vertebral body.

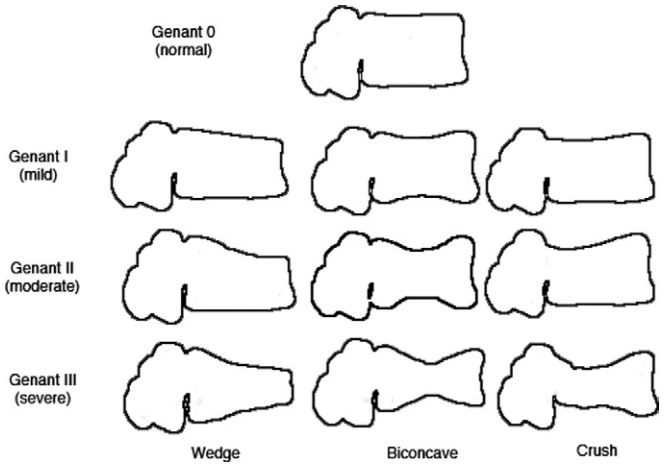

Figure. Genant scoring system for vertebral fractures.

All study subjects also underwent BMD of the lumbar spine measured with the Hologic 4500A DXA. Each BMD was converted to a z-score by using the manufacturer's standard pediatric reference range. We also determined the volumetric BMD (vBMD) for subjects >7.5 years old and converted it to a z-score,[18] allowing correction of the BMD for stature. When fractures involved the L2 to L4 region, the BMD was calculated excluding the affected vertebra(e).

Statistical analyses were performed with SAS software version 9.1 (SAS Institute, Carey, North Carolina). Two patients with vertebral fractures were missing dietary assessment of total daily calcium and vitamin D intake, for which we performed multiple imputations with SAS PROC MI. In brief, missing values of total daily calcium and vitamin D intake were imputed (m = 10 replicates, method = regression). For the imputation, independent predictors were the same variables used in the Poisson and multivariate regressions described below. Both of these regression techniques were then applied to each of the imputed datasets, and the results were formally pooled in SAS PROC MIANALYZE to provide unbiased parameter estimates that properly reflected the uncertainty associated with missing data.[19]

The Mann-Whitney *U* test was used to test significance for median differences in baseline characteristics and risk factors between the fracture and non-fracture group. We used multivariate Poisson count regression analysis to identify pos-