

# Bone Health and Growth in Glucocorticoid-Treated Patients with Juvenile Idiopathic Arthritis

HELENA VALTA, PEKKA LAHDENNE, HANNU JALANKO, KRISTIINA AALTO, and OUTI MÄKITIE

**ABSTRACT. Objective.** To evaluate bone health and growth and their correlates in glucocorticoid (GC)-treated pediatric patients with juvenile idiopathic arthritis (JIA).

**Methods.** Consecutive patients with a history of JIA for  $\geq 2$  years and systemic GC treatment for  $\geq 3$  months were assessed for bone health and its determinants. Areal bone mineral density (aBMD) and vertebral body morphology were assessed with DEXA; Z scores were adjusted for calendar and bone age. Values were correlated with biochemistry, disease activity, and medications.

**Results.** Sixty-two patients (43 female; median age 11.8 yrs, median disease duration 5.6 yrs) were included. The median duration of GC treatment was 24 months and the median cumulative dose (as prednisolone) was 2.2 g. Four patients had had fractures. The median bone age-corrected aBMD Z score was  $-0.4$  (range  $-2.9$  to  $+1.8$ ) for lumbar spine and  $-0.1$  (range  $-2.1$  to  $+2.4$ ) for femoral neck. Abnormal vertebral morphology was observed in 6 patients (10%). No correlation was found between aBMD and disease characteristics or cumulative GC dose. The median Z score for height was  $+0.1$  (range  $-2.9$  to  $+1.5$ ) and the median height-adjusted weight  $+4\%$  (range  $-17\%$  to  $+40\%$ ).

**Conclusion.** Our study showed low prevalence of osteoporosis and normal growth in children with JIA. However, asymptomatic vertebral fractures were observed in 10% of the patients, indicating that DEXA alone may not be sufficient when evaluating bone health in these children. Osteoporosis still remains a concern in children with GC-treated JIA. (First Release Feb 15 2007; J Rheumatol 2007;34:831-6)

## Key Indexing Terms:

JUVENILE IDIOPATHIC ARTHRITIS  
FRACTURES

GROWTH

OSTEOPOROSIS  
GLUCOCORTICIDS

Previous reports have associated juvenile idiopathic arthritis (JIA) with detrimental changes in bone metabolism: secondary osteopenia and osteoporosis as well as growth retardation have been documented<sup>1-4</sup>. Several factors may have a negative impact on bone health in JIA. Chronic inflammation may result in periarticular and generalized bone loss<sup>5,6</sup>. Cytokines and growth factors produced by synovial tissue may increase osteoclast formation, activity, and/or survival and thus increase bone resorption<sup>7</sup>. In patients with JIA the limited physical functioning and reduced muscle forces acting on bone may pose an additional risk for osteoporosis<sup>8,9</sup>.

Medications, especially glucocorticoids (GC), have been regarded as the main threat for skeletal health in patients with

JIA. They enhance bone resorption and reduce bone formation<sup>10</sup>. This may result in symptomatic osteoporosis even in children<sup>11,12</sup>. Methotrexate (MTX) has been reported to cause osteopenia when used in the treatment of childhood malignancies<sup>13</sup>. The dosing in JIA is substantially lower and does not seem to have adverse effects on bone<sup>14,15</sup>.

Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is known to be an important mediator in inflammatory conditions. The new TNF- $\alpha$  antagonists may prevent bone loss directly by regulating osteoclast formation and activation or by decreasing the amount of circulating cytokines<sup>16,17</sup> and indirectly by allowing for reduced GC dosing and improved physical activity<sup>6,18,19</sup>.

We evaluated growth and bone health in children with JIA who have been treated with GC and multiple drug combinations. The results suggest that systemic skeletal complications of the active disease and medications still remain a concern in children with JIA.

## MATERIALS AND METHODS

**Study population.** Sixty-two patients with JIA, diagnosed according to the revised criteria for JIA<sup>20</sup>, were included in this prospective study at the Hospital for Children and Adolescents, Division of Pediatric Rheumatology, Helsinki University Hospital. The hospital is a tertiary referral center for pediatric rheumatology patients. The annual incidence of JIA in this region is up to 21/100,000<sup>21</sup>. The study protocol was approved by the Helsinki University Hospital Ethics Committee and a written informed consent was obtained from all the patients and/or parents.

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**Study design.** The study included consecutive patients, who (1) fulfilled the revised criteria for JIA<sup>20</sup> and were followed at the Pediatric Rheumatology Outpatient Clinic, Helsinki University Hospital, since diagnosis; (2) were between 4 and 18 years of age; (3) were diagnosed with JIA at least 2 years prior to the study; and (4) had been treated with systemic GC for  $\geq 3$  months. Of the 66 patients fulfilling the inclusion criteria, 62 (94%) consented and 4 (6%) refused because of social reasons or lack of interest.

**Clinical characteristics.** Medical records were reviewed for disease and treatment characteristics and for growth and fractures. Orally administered GC were converted to prednisolone equivalents, and absolute and weight-adjusted (dose per body weight) cumulative doses of prednisolone were calculated for each patient. The patients or their parents filled out questionnaires on the patient's physical activity and fracture history and on the child's well-being. The localization of the reported fractures and the mechanism of injury (low or high energy, e.g., falling > 3 m or traffic accident) were recorded. A 3 day dietary recall was obtained for each patient: the patients or their parents were asked to record the trade names and amounts of all food items and beverages consumed during 2 work days and one day of the weekend. Based on these recordings, the average daily intake of calcium (Ca) and vitamin D were calculated for each patient using a computer program, AIVO 2000 – Diet32, version 1.4.2.1, based on the Finnish dietary references for 1998<sup>22</sup>.

The patients were assessed clinically by a pediatric rheumatologist (PL or KA). Global assessment of overall well-being by the parents, physician's global assessment of disease activity, and Childhood Health Assessment Questionnaire (CHAQ) were determined. Inactive disease on medication was defined as suggested by Wallace, *et al*<sup>23</sup>.

**Growth assessment.** Height was measured with a Harpenden stadiometer (Holtain Limited, UK) and weight was measured in thin underwear with an electric scale; values were compared with Finnish growth charts<sup>24,25</sup>. In addition, heights obtained at previous clinic visits were collected from hospital records and compared with norms. Height standard deviation (SD) score (height Z score) was defined as deviation of height, in SD units, from mean height for age and sex<sup>24</sup>. Weights were expressed as height-adjusted values, in percentages of the mean ratio in the normal population of same sex and height, according to the Finnish standards<sup>24,25</sup>. Pubertal maturation was assessed according to Tanner<sup>26</sup>.

**Biochemistry.** Blood biochemistry was obtained for blood erythrocyte sedimentation rate (ESR), for plasma Ca, inorganic phosphate (Pi), alkaline phosphatase (ALP), parathyroid hormone (PTH), creatinine (Cr), and for serum concentrations of 25-hydroxyvitamin D (25-OH-D), insulin-like growth factor-1 (IGF-1), and IGF binding protein 3 (IGFBP-3). Girls over age 8 years and boys over 10 years were assessed also for gonadotrophins and sex steroids (follicle-stimulating hormone, luteinizing hormone, and estradiol or testosterone). Urine was analyzed for Ca to Cr ratio. P-Ca, P-Pi, P-ALP, f-PTH and S-25-OH-D, and urine Ca and Cr were determined by standard assays. Reference ranges for P-Pi and P-Cr were age-dependent and, for P-ALP, age- and sex-dependent; the measured values were transformed into SD scores (Z scores) using normal values to allow for cross-sectional comparison.

**Imaging studies.** A plain radiograph of the left hand was obtained and bone age determined according to Greulich-Pyle<sup>27</sup>. It was considered normal if it differed less than 1.0 year from the calendar age. Bone mineral content (BMC, g) and areal bone mineral density (aBMD, g/cm<sup>2</sup>) of the lumbar spine (L1-L4), left femoral neck, total hip, and whole body were assessed with dual-energy x-ray absorptiometry (DEXA) bone densitometry (Discovery A, software version 12.01:3; Hologic Inc., Waltham, MA, USA). All measured values were transformed into Z scores using the equipment-specific age- and sex-adjusted reference database for US Caucasian children. In the absence of a Finnish national database, these reference data were considered appropriate, first because the heights of US children do not differ significantly from Finnish children of same age and sex<sup>24,28</sup>, and second because BMD and its variation in young Finnish adults is similar to that in the US Caucasian reference population (unpublished observation, Hologic Inc.). Whole-body lean tissue mass (LTM) and BMC were obtained by DEXA and BMC/LTN ratio

calculated for both height and age according to Höglér, *et al*, and the results were transformed into Z scores<sup>29</sup>. The DEXA scanner can also produce lateral and posteroanterior images of the spine (Instant Vertebral Assessment, IVA) from T4 to L5 to detect vertebral compression fractures. IVA images were obtained for all the patients. If the lumbar BMD Z score was  $\leq -2.0$  or if a spinal compression fracture was suspected in the IVA images, standing posteroanterior and lateral plain radiographs of the spine were also obtained. The IVA images and spinal radiographs were assessed independently by authors OM and HV for the presence of spinal compression deformities; discordant readings were reanalyzed for consensus and borderline cases were classified as normal. The vertebral changes were classified as normal, mild, or severe anterior wedge deformity or mild or severe compression deformity according to the classification by Mäkitie, *et al*<sup>30</sup>; a height reduction of 20% in the anterior or middle vertebral height was considered significant and height reductions of less than 20% were regarded as normal. If compression fractures were observed in the lumbar spine the affected vertebrae were omitted from the assessment of aBMD.

**Statistical analysis.** Simple regression analysis, Student's unpaired t-test, and chi-square test were used, as appropriate, for statistical analysis (Statview® 5.0.1 for Macintosh, 1992-98; SAS Institute Inc., Cary, NC, USA). A p value < 0.05 was considered statistically significant.

## RESULTS

**Patient and disease characteristics.** Demographic data and clinical characteristics of the 62 children with JIA are given in Table 1. Disease activity at the time of the study assessment

Table 1. Demographic data and clinical characteristics of the 62 patients with JIA.

Study subjects	
Males/females (%)	19 (31)/43 (69)
Age, median (range), yrs	11.8 (4.6–17.9)
Age at disease onset, median (range), yrs	4.0 (1.1–15.3)
Disease duration, median (range), yrs	5.6 (2.0–15.1)
Systemic onset (%)	2 (3)
HLA-B27-positive (%)	19 (31)
ANA antibody-positive (%)	15 (24)
History of uveitis (%)	20 (32)
JIA subtype, n (%)	
Systemic arthritis	2 (3)
Persistent oligoarthritis	10 (16)
Extended oligoarthritis	16 (26)
Polyarthritis, RF-negative	33 (53)
Polyarthritis, RF-positive	1 (2)
Psoriatic arthritis	0 (0)
Enthesitis related arthritis	2 (3)
Anthropometric characteristics at study assessment	
Height Z scores, median (range)	+0.10 (–2.9 to +1.5)
Height-adjusted weight, % median (range)	+4 (–17 to +40)
Prepubertal (Tanner stage 1) (%)	27 (44)
Pubertal (Tanner stage 2–3) (%)	20 (32)
Postpubertal (Tanner stage 4–5) (%)	15 (24)
Disease activity at study assessment, mean (range)	
Physician's global assessment of disease activity*	1.0 (0–8)
CHAQ**	0.2 (0–1.6)
Parent's global assessment of child's well-being*	1.1 (0–8.7)
No. joints with active disease†	0.8 (0–8)
No. joints with limited range of motion†	1.3 (0–8)
Erythrocyte sedimentation rate, mm/h	13 (2–65)

\* Visual analog scale (0–10 cm), 0 = best and 10 = worst. \*\* Childhood Health Assessment Questionnaire, score 0–3, 0 = best and 3 = worst. † 75 joints were evaluated per patient.

varied among the patients (Table 1). Thirty-four patients (55%) were in clinical remission and taking medication. All patients were taking antirheumatic drugs at study assessment.

**Ca and vitamin D.** Twenty patients (32%) had been prescribed vitamin D supplement (10–20 µg or 400–800 IU daily), and of these, 9 patients (15%) were also taking Ca supplement (500–1000 mg daily). The mean Ca intake of the study subjects was 1350 mg per day (range 385–2560 mg) or 169% of the recommended intake; it was below the recommendation in 10 (16%) patients. The mean daily vitamin D intake was 7.9 µg (316 IU; range 1.1–30.1 µg), corresponding to 157% of the intake recommended in Finland at the time of the study; the intake was less than recommended in 23 (37%) patients.

**Physical activity.** The majority of the patients (90%) participated in normal physical education at school. In addition, 35 patients (56%) had a regular, at least once weekly, leisure time weight-bearing physical activity of at least 45 min duration.

**Medications.** During the course of their illness all patients had been taking systemic GC treatment for at least 3 months. Twelve patients (19%) had been taking combination therapy of GC and MTX only, while 50 patients (81%) had taken 1–6 drugs in addition to GC and MTX. Forty-three patients (63%) had been taking GC during the 2 years preceding the study. TNF-α antagonists had been taken since 1999 by 20 (32%) patients with treatment-resistant JIA; 17 patients (27%) had received TNF-α antagonists during the 2 years preceding the study.

The median duration of systemic GC treatment was 24 months (range 3–152 mo). Fifty-four patients (87%) had been on an alternate-day regimen for more than 90% of the total duration of their GC treatment. The median cumulative dose of GC, calculated as prednisolone, was 2.2 g (range 0.2–21.2 g). The median cumulative weight-adjusted dose was 88 mg/kg (range 11–1095 mg/kg). Both the total cumulative GC dose ( $p = 0.022$ ) and the weight-adjusted GC dose ( $p = 0.017$ ) were significantly higher in patients with polyarticular disease than in those with oligoarticular disease. Patients treated with TNF-α antagonists had significantly higher mean duration (1993 vs 734 days;  $p < 0.001$ ) and mean cumulative weight-adjusted dose (387 vs 99 mg/kg;  $p < 0.001$ ) of GC than patients not taking TNF-α antagonists. Intraarticular corticosteroids had been administered to 58 patients (94%); the median number of injections given was 8 (range 1–37). The drugs taken by subjects at the time of assessment are listed in Table 2.

**Anthropometry.** Most of the patients were of normal stature at study assessment (height Z score  $-2.0$  to  $+2.0$  and height-adjusted weight  $-15\%$  to  $+20\%$ ). The median height Z score was  $+0.1$  and the median height-adjusted weight  $+4\%$ . Two patients (3%) had a height Z score below  $-2.0$  ( $-2.4$  and  $-2.9$ ). The height-adjusted weight was more than 20% above the population mean for height and sex in 9 patients (15%) and more than 20% below the population mean in none of the patients. The median height Z scores at disease onset and annually during followup are shown in Figure 1.

Table 2. Drugs taken by the 62 study subjects with JIA at the time of study assessment.

Therapeutic Agent	Patients N (%)
Methotrexate	49 (79)
Glucocorticoid	26 (42)
TNF-α antagonist	17 (27)
Infliximab	8
Adalimumab	5
Etanercept	4
Hydroxychloroquine	15 (24)
Leflunomide	5 (8)
Sulfasalazine	2 (3)

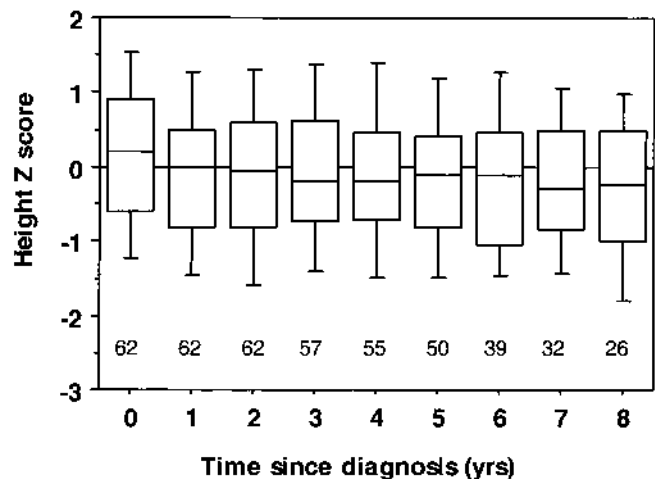


Figure 1. Linear growth since diagnosis in 62 patients with JIA. The bottom of each box indicates the first, the cross line the second (median), and the top the third quartile of the variables. Whiskers extend from the box to the highest and lowest values, excluding outliers. Numbers of observations at each timepoint are indicated above the x-axis.

**Fractures.** Four patients (6%) had had a nonvertebral fracture after the diagnosis of JIA: 2 clavicle, 1 wrist, and 1 metatarsal fracture were recorded. All these fractures had resulted from low energy injuries. No previously diagnosed compression fractures were reported.

**Biochemistry.** The median P-Ca was 2.40 mmol/l; one patient had mild hypocalcemia. One patient had P-Pi below the age-adjusted reference value (0.74 mmol/l). Hyperphosphatemia was not observed in any patient. The fP-PTH was within normal range (8–73 ng/l) in all but one patient who had supranormal fP-PTH (98 ng/l). Six patients (10%) were hypercalciuric (urine Ca:Cr ratio  $\geq 0.7$  mmol/mmol). The median S-25-OHD was 49 nmol/l and it was  $\leq 37$  nmol/l in 16 patients (26%). Concentrations of gonadotrophins and sex steroids were in accord with pubertal status and no patient had evidence of hypogonadism. The median Z score for P-ALP was  $-0.5$  (range  $-1.9$  to  $+2.3$ ).

**Imaging studies.** Most of the patients had aBMD Z scores

between  $\pm 2$  SD of the reference values for the lumbar spine, hip, and whole body in DEXA assessment (Table 3, Figure 2). Since bone age was delayed by  $\geq 1.0$  year in 15 patients (24%) and advanced by  $\geq 1.0$  year in 12 patients (19%), the aBMD Z scores were calculated for both calendar age and for bone age (Table 3). The median bone age-adjusted aBMD Z score was  $-0.4$  for lumbar spine,  $-0.1$  for hip, and  $-0.1$  for the whole body. The lumbar spine Z score was significantly reduced ( $p = 0.01$ ) as compared with the expected median Z score value of 0.0. The bone age-adjusted aBMD Z score was below  $-1.0$  and below  $-2.0$  at the lumbar spine in 12 (19%) and in 3 patients (5%), respectively, and at the hip in 13 patients (21%) and in 1 patient (2%), respectively. The median BMC/LTM ratio Z score for height was  $-0.20$  (range  $-2.6$  to  $+1.6$ ) and for age 0.23 (range  $-2.4$  to  $+1.25$ ); the Z scores for height or age were below  $-1.0$  in 15 and 6 subjects, respectively.

IVA images were available for all 62 patients. In addition, standard radiographs of the thoracic and lumbar spine were also available for 10 patients. Abnormal vertebral morphology, suggesting compression fractures, was observed in 6 patients (10%), 3 male and 3 female, ranging in age from 8.2 to 15.4 years (mean 12.8 yrs). Five patients had anterior wedge deformity and one patient, a compression deformity affecting the anterior, middle, and posterior heights of the vertebrae. Only one of these patients had compression fractures affecting lumbar region L1-L4; his aBMD was not included in the further data analysis. Four of the 6 patients with vertebral changes had polyarticular, one had extended oligoarticular, and one oligoarticular JIA. Their mean disease duration was 5.0 years (2.7–8.2 yrs), mean height Z score at study assessment  $+0.4$  ( $-0.8$  to  $+1.2$ ), mean height-adjusted weight 14.7% ( $-6\%$  to  $+49\%$ ), and mean cumulative GC dose 3.1 g (0.8–8.5 g), or 120 mg/kg (23–443 mg/kg). Three of the 6 had been treated with TNF- $\alpha$  antagonists. Their mean daily Ca intake was 1348 mg and mean vitamin D intake 7.9  $\mu\text{g}$ . There was no statistically significant difference in the duration of GC treatment ( $p = 0.358$ ) or weight-adjusted cumulative GC dose ( $p = 0.433$ ) in patients with abnormal vertebral findings as compared with patients with normal vertebral morphology. None of the 6 patients had calendar age or bone age-adjusted aBMD Z scores below  $-2.0$ .

*Correlates of bone health.* Patients with longer disease duration tended to have lower bone age and calendar age-adjusted

aBMD Z scores at the hip but not in the lumbar spine. No correlation was found between any of the aBMD measures and the age at disease onset. There was no difference in bone age or calendar age-adjusted aBMD measures, nor in any of the biochemical measures, between patients with polyarticular or oligoarticular disease. The aBMD values adjusted for bone age or calendar age in the femoral neck or lumbar spine did not correlate with disease activity at the time of the study.

There was no correlation among the number of intraarticular corticosteroid injections, markers of disease activity (Table 1), biochemical measures, or vitamin D or Ca intake and any of the bone age or calendar age-adjusted aBMD Z scores.

Neither the total duration of GC treatment nor the weight-adjusted cumulative GC dose showed significant correlation with any of the aBMD measures. Further, no significant difference in the aBMD values was found between the 26 patients who were taking steroid treatment, or the 17 patients who were taking anti-TNF treatment at the time of DEXA, and the rest of the study subjects. The calendar age ( $r = 0.74$ ,  $p < 0.0001$ ) and bone age ( $r = 0.52$ ,  $p < 0.001$ ) adjusted aBMD Z scores at the hip and lumbar spine correlated with each other. A strong positive correlation was observed between the Z score for height and the calendar age-adjusted aBMD Z scores for total hip ( $r = 0.37$ ) and lumbar spine ( $r = 0.53$ ) ( $p < 0.005$  for both).

## DISCUSSION

Recent years have brought significant changes to the therapy of JIA with the introduction of new antirheumatic drugs. While several previous reports have found a high prevalence of osteopenia and osteoporosis in patients with JIA<sup>3,4,31</sup>, our results suggest that the presently used treatment modalities have resulted in improved overall skeletal health in children with JIA. However, subnormal BMD readings as well as vertebral compression fractures were also detected in our cohort. These are evidence for the significant potential risks of JIA to normal bone health.

The skeletal health of patients in our study was evaluated by fracture history and DEXA assessment. In addition to conventional BMD assessment, lateral spinal images were obtained to identify spinal compression fractures<sup>30</sup>. The BMD values were corrected for bone age to avoid misinterpretation of the results. The results suggest that only a minority of the

Table 3. Bone mineral density (BMD) measurements, obtained by DEXA, for the 62 patients with JIA. Data are median (range).

	Lumbar Spine (L1–L4)	Total Hip	Femoral Neck	Whole Body
aBMD, g/cm <sup>2</sup>	0.685 (0.413–1.114)	0.719 (0.464–1.173)	0.664 (0.420–1.079)	0.740 (0.561–1.065)
aBMD Z score	$-0.1$ ( $-2.9$ to $+2.2$ )	$0.0$ ( $-2.4$ to $+2.0$ )	$-0.3$ ( $-2.3$ to $+1.5$ )	$-0.2$ ( $-2.4$ to $+2.4$ )
aBMD Z score corrected for bone age	$-0.4$ ( $-2.9$ to $+1.8$ )	$-0.1$ ( $-2.1$ to $+2.4$ )		$-0.1$ ( $-1.9$ to $+2.4$ )

aBMD: areal bone mineral density.

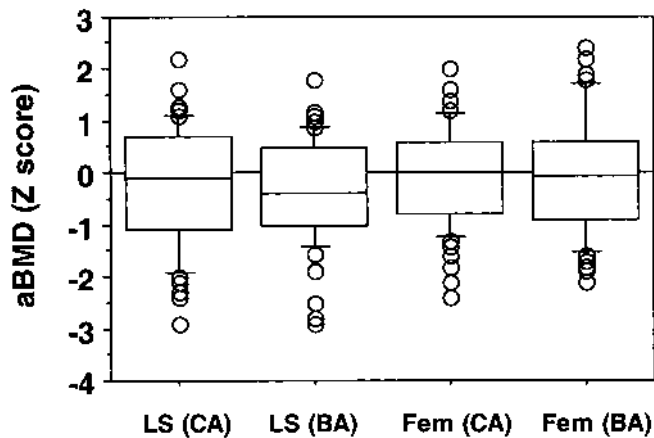


Figure 2. Areal BMD values for the 62 patients with JIA. The bottom of each box indicates the first, the cross line the second (median), and the top the third quartile of the variables. Whiskers extend from the box to the highest and lowest values, excluding outliers. LS: lumbar spine; Fem: femoral head; CA: calendar age-adjusted; BA: bone age-adjusted.

children treated for JIA with the presently available drug combinations develop significant osteopenia or symptomatic osteoporosis. Further, most of these patients were of normal stature and only 2 patients had a height Z score below the population reference values.

The study group did, however, include 6 children with asymptomatic vertebral compression fractures that can be regarded as a sign of significant secondary osteoporosis. Further, the median aBMD Z score for the lumbar spine, although well above  $-1.0$ , was below the population mean for age and sex, further evidence that the underlying illness and the medical treatment have adverse effects on the skeleton. In a recent study, 196 children with a history of solid organ transplant were similarly assessed for growth, BMD, and fractures<sup>32</sup>. The study showed a high prevalence of growth retardation and osteoporosis, and a several-fold increased prevalence of peripheral and vertebral fractures in the transplant patients<sup>32</sup>. When compared with the observations in the transplant patients, the present study group of children with JIA showed significantly fewer skeletal complications. However, the vertebral fracture rate was still higher than in a healthy pediatric population. No previous study on JIA systematically evaluated the subjects for the presence of compression fractures, and the overall prevalence and risk factors of these skeletal complications remain largely unknown.

GC are known to have a strong negative influence on bone metabolism. The increased bone resorption may be the result of decreased intestinal Ca absorption, increased urinary Ca excretion, or of decreased gonadotrophin, sex steroid, and IGF-I synthesis<sup>33</sup>. With extended exposure to steroids the osteoblast function also decreases<sup>10</sup>. In our study, the duration of systemic GC treatment varied from 3 months to 12.5 years and mainly alternate-day dosing was used. An alternate-day steroid regimen may induce fewer GC side effects than the

daily regimen<sup>34-36</sup>. The use of alternate-day steroid regimen may partly explain the good linear growth and normal pubertal development in the majority of our patients. In addition to dosing, other factors, such as individual variability in GC-metabolizing enzymes in osteoblasts<sup>37</sup> and steroid hormone receptor polymorphisms<sup>38</sup>, may influence the degree of steroid-induced bone loss.

TNF- $\alpha$  is a major cytokine mediating inflammation in JIA; it also stimulates osteoclastogenesis and simultaneously inhibits osteoblast function<sup>39</sup>. The favorable treatment response to TNF- $\alpha$  antagonists is likely to result not only in reduced symptoms and overall disease activity but also in a more favorable balance between osteoclast and osteoblast function. Further, the reduced disease activity allows for lower dosing or discontinuation of systemic GC and improved physical activity of the patients. Our findings are in line with the suggested beneficial skeletal effects of TNF- $\alpha$  antagonists, but the cross-sectional study setting and small number of patients do not allow for any detailed conclusions.

Vitamin D plays an important role in Ca homeostasis. Several studies have shown a high prevalence of subclinical vitamin D deficiency in Finland<sup>40,41</sup>. In our study, 26% of the patients had a S-25-OH-D value below 37.5 nmol/l despite an average vitamin D intake corresponding to 157% of the recommended daily intake of 5  $\mu$ g. The vitamin D concentrations in our study subjects were similar to those shown in the general Finnish population<sup>40,41</sup>. In October 2005 the Finnish recommendation for vitamin D intake was increased to 7.5  $\mu$ g daily. It is not yet known whether even this higher dose sufficiently increases vitamin D levels. These preventive measures are of great importance, especially in chronically ill children who are at increased risk of developing osteoporosis<sup>42</sup>.

Childhood weight-bearing physical activity has been recognized as a significant determinant of peak bone mass<sup>43,44</sup>. There are only a few studies addressing the influence of weight-bearing exercise programs on bone health in patients with rheumatoid arthritis. In our cohort, good control of disease activity had allowed normal physical activity in most of the patients, over 90% of the subjects being able to attend the normal school based physical education program. It is likely that the improved disease control also contributes to bone health by allowing for increased weight-bearing exercise.

Our study showed reductions in aBMD and a 10% prevalence of vertebral compression fractures in GC-treated children with JIA. Despite the satisfactory average BMD and height Z scores, the high prevalence of vertebral fractures indicates that osteoporosis remains a concern in children with JIA. More attention needs to be paid to preventive measures such as optimizing vitamin D and Ca intake and encouraging weight-bearing physical activity in patients with satisfactory disease control. Compression fractures may be present even in asymptomatic patients. Systematic followup for bone health, including DEXA and spinal imaging, is recommended for children treated with JIA.

## REFERENCES

- Simon D, Fernando C, Czernichow P, Prieur AM. Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. *J Rheumatol* 2002;29:1296-300.
- Wang SJ, Yang YH, Lin YT, Yang CM, Chiang BL. Attained adult height in juvenile rheumatoid arthritis with or without corticosteroid treatment. *Clin Rheumatol* 2002;21:363-8.
- Celiker R, Bal S, Bakkaloglu A, et al. Factors playing a role in the development of decreased bone mineral density in juvenile chronic arthritis. *Rheumatol Int* 2003;23:127-9.
- Lien G, Flato B, Haugen M, et al. Frequency of osteopenia in adolescents with early-onset juvenile idiopathic arthritis: a long-term outcome study of one hundred five patients. *Arthritis Rheum* 2003;48:2214-23.
- Haugeberg G, Orstavik RE, Kvien TK. Effects of rheumatoid arthritis on bone. *Curr Opin Rheumatol* 2003;15:469-75.
- Strand V, Kavanaugh AF. The role of interleukin-1 in bone resorption in rheumatoid arthritis. *Rheumatology Oxford* 2004;43:10-6.
- Gravallese EM. Bone destruction in arthritis. *Ann Rheum Dis* 2002;61:84-6.
- Hakkinen A, Sokka T, Kautiainen H, Kotaniemi A, Hannonen P. Sustained maintenance of exercise induced muscle strength gains and normal bone mineral density in patients with early rheumatoid arthritis: a 5 year follow up. *Ann Rheum Dis* 2004;63:910-6.
- Lindehammar H, Lindvall B. Muscle involvement in juvenile idiopathic arthritis. *Rheumatology Oxford* 2004;43:1546-54.
- Canalis E. Mechanisms of glucocorticoid-induced osteoporosis. *Curr Opin Rheumatol* 2003;15:454-7.
- Bianchi ML. Glucocorticoids and bone: some general remarks and some special observations in pediatric patients. *Calcif Tissue Int* 2002;70:384-90.
- Boling EP. Secondary osteoporosis: underlying disease and the risk for glucocorticoid-induced osteoporosis. *Clin Ther* 2004;26:1-14.
- Mandel K, Atkinson S, Barr RD, Pencharz P. Skeletal morbidity in childhood acute lymphoblastic leukemia. *J Clin Oncol* 2004;22:1215-21.
- Cranney AB, McKendry RJ, Wells GA, et al. The effect of low dose methotrexate on bone density. *J Rheumatol* 2001;28:2395-9.
- Cimaz R. Osteoporosis in childhood rheumatic diseases: prevention and therapy. *Best Pract Res Clin Rheumatol* 2002;16:397-409.
- Feng X. Regulatory roles and molecular signaling of TNF family members in osteoclasts. *Gene* 2005;350:1-13.
- Saidenberg-Kermanac'h N, Corrado A, Lemeiter D, deVernejoul MC, Boissier MC, Cohen-Solal ME. TNF-alpha antibodies and osteoprotegerin decrease systemic bone loss associated with inflammation through distinct mechanisms in collagen-induced arthritis. *Bone* 2004;35:1200-7.
- Lahdenne P, Vahasalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. *Ann Rheum Dis* 2003;62:245-7.
- Simonini G, Giani T, Stagi S, de Martino M, Falcini F. Bone status over 1 yr of etanercept treatment in juvenile idiopathic arthritis. *Rheumatology Oxford* 2005;44:777-80.
- Petty RE, Southwood TR, Manners P, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390-2.
- Berntson L, Andersson Gare B, Fasth A, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. *J Rheumatol* 2003;30:2275-82.
- National Nutrition Council 1998, the Finnish Nutrition Recommendations, Committee report 1998:7. Helsinki: Oy Edita ab. ISBN 951-53-2054-2.
- Wallace CA, Ruperto N, Giannini E, Childhood Arthritis and Rheumatology Research Alliance, Pediatric Rheumatology International Trials Organization, Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290-4.
- Sorva R, Lankinen S, Tolppanen EM, Perheentupa J. Variation of growth in height and weight of children. II. After infancy. *Acta Paediatr Scand* 1990;79:498-506.
- Pere A. Comparison of two methods for transforming height and weight to normality. *Ann Hum Biol* 2000;27:35-45.
- Tanner JM, editor. Growth at adolescence. Oxford, UK: Blackwell Scientific Publications; 1962.
- Greulich WW, Pyle SI. Radiographic atlas of the skeletal development of the hand and wrist. 2nd ed. Palo Alto, CA: Stanford University Press; 1959.
- Kuczmariski RJ, Ogden CL, Grummer-Strawn LM, et al. CDC growth charts: United States. *Adv Data* 2000;314:1-27.
- Hogler W, Briody J, Woodhead HJ, Chan A, Cowell CT. Importance of lean mass in interpretation of total body densitometry in children and adolescents. *J Pediatr* 2003;143:81-8.
- Makitie O, Doria AS, Henriques F, et al. Radiographic vertebral morphology: a diagnostic tool in pediatric osteoporosis. *J Pediatr* 2005;146:395-401.
- McDonagh JE. Osteoporosis in juvenile idiopathic arthritis. *Curr Opin Rheumatol* 2001;13:399-404.
- Helenius I, Remes V, Salminen S, et al. Incidence and predictors of fractures in children after solid organ transplantation: a 5-year prospective, population-based study. *J Bone Miner Res* 2006;21:380-7.
- Canalis E, Giustina A. Glucocorticoid-induced osteoporosis: summary of a workshop. *J Clin Endocrinol Metab* 2001;86:5681-5.
- Jabs K, Sullivan EK, Avner ED, Harmon WE. Alternate-day steroid dosing improves growth without adversely affecting graft survival or long-term graft function. A report of the North American Pediatric Renal Transplant Cooperative Study. *Transplantation* 1996;61:31-6.
- Hiraoka M, Tsukahara H, Matsubara K, et al. A randomized study of two long-course prednisolone regimens for nephrotic syndrome in children. *Am J Kidney Dis* 2003;41:1155-62.
- Vidhun JR, Sarwal MM. Corticosteroid avoidance in pediatric renal transplantation. *Pediatr Nephrol* 2005;20:418-26.
- Cooper MS. Sensitivity of bone to glucocorticoids. *Clin Sci (London)* 2004;107:111-23.
- Gennari L, Becherini L, Falchetti A, Masi L, Massart F, Brandi ML. Genetics of osteoporosis: role of steroid hormone receptor gene polymorphisms. *J Steroid Biochem Mol Biol* 2002;81:1-24.
- Nanes MS. Tumor necrosis factor-alpha: molecular and cellular mechanisms in skeletal pathology. *Gene* 2003;321:1-15.
- Lehtonen-Veromaa MK, Mottonen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. *Am J Clin Nutr* 2002;76:1446-53.
- Valimaki VV, Alfthan H, Lehmuskallio E, et al. Vitamin D status as a determinant of peak bone mass in young Finnish men. *J Clin Endocrinol Metab* 2004;89:76-80.
- Sochett EB, Makitie O. Osteoporosis in chronically ill children. *Ann Med* 2005;37:286-94.
- Fuchs RK, Bauer JJ, Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. *J Bone Miner Res* 2001;16:148-56.
- MacKelvie KJ, Khan KM, Petit MA, Janssen PA, McKay HA. A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomized controlled trial in girls. *Pediatrics* 2003;112:e447-52.