Bone Mass Development and Bone Metabolism in Juvenile Idiopathic Arthritis: Treatment with Growth Hormone for 4 Years

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ABSTRACT. ***Objective.*** To study the acquisition of bone mass and changes in bone mineral density (BMD) related to age, bone age, pubertal status, and growth hormone (GH) therapy in 11 children with juvenile idiopathic arthritis (JIA) longitudinally over 4 years, in comparison to healthy children.

Methods. Bone mineral content (BMC), BMD, and vertebral area were measured by dual energy x-ray absorptiometry. Since BMC and BMD increase with size, BMD was converted to volumetric BMD (vBMD) after adjustment for vertebral size.

Results. At inclusion all patients (7 female, 4 male, mean age 10.3 ± 2.1 yrs) had low BMD, with a mean z-score for area BMD (aBMD) of -2.04 ± 0.8 SD. After adjustment for size, vBMD was 0.198 g/cm^3, and after 4 years of GH treatment it increased significantly to 0.232 g/cm^3 (p < 0.03), expressed as SD scores that increased from -2.97 ± 0.81 SD to -2.83 ± 0.67 SD. In relation to bone age, vBMD SD increased from -2.53 ± 0.85 to -2.41 ± 0.79. Compared to pretreatment values, bone formation and resorption markers increased significantly during treatment.

Conclusion. Our results reflect an increase in bone turnover under GH therapy in these patients. Despite biochemical changes there was a stabilization of vBMD for age and bone age, with a percentage increase comparable to healthy children. Longterm GH treatment will be necessary to evaluate a potential positive effect of GH on bone density and metabolism in patients with JIA. (J Rheumatol 2004;31:1407–12)

Key Indexing Terms:
JUVENILE IDIOPATHIC ARTHRITIS   OSTEOPOROSIS   BONE METABOLISM
VOLUMETRIC BONE MINERAL DENSITY   GROWTH HORMONE

Osteopenia and osteoporosis are characterized by loss of both bone mass and microarchitectural integrity of the skeleton, which leads to bone fragility and risk of fractures[1]. An increased frequency of fractures, such as vertebral collapse, has been described in children with juvenile chronic arthritis (JCA)[2]. The major factors associated with osteopenia and growth retardation in juvenile arthritis appear to be disease activity and the necessary medication, especially glucocorticoids. Even when the lowest possible dose of glucocorticoid is used to control the disease, side effects are not uncommon. It is a matter of discussion whether osteoporosis is more closely related to mean daily dose or total cumulative dose[2,3].

Studies on growth hormone (GH) treatment in GH deficient children can show, in addition to an increase of height,

an effect of GH on bone mass and mineral metabolism. There are also reports on short term effects of GH on height and bone in JCA[4,5]. Is there a longterm beneficial effect of GH on bone in patients with juvenile arthritis?

To our knowledge there are no reports documenting changes of axial bone mineral density (BMD) longitudinally in children with juvenile idiopathic arthritis (JIA) during GH treatment. Since the densitometric data obtained by dual energy x-ray absorptiometry (DEXA) are greatly influenced by bone size[6], the growth of the children must be taken into account in longitudinal studies. Radiographs alone underestimate the frequency of osteoporosis, as more than 30% of bone mass is already lost before the appearance of radiographic signs of osteoporosis[7].

We investigated the magnitude of increase of lumbar area BMD (aBMD) and volumetric BMD (vBMD) of children with JIA during GH treatment over a period of 4 years. We also assessed the effect of GH on biochemical markers of bone metabolism in these children undergoing longterm glucocorticoid therapy. Studies on markers of bone mineral metabolism show that children with juvenile rheumatoid arthritis (JRA) had lower serum calcium concentration, but data on urinary excretion of calcium and vitamin D and intact parathyroid hormone (PTH) are conflicting[8,9].

We have reported the beneficial effect of recombinant

human GH on growth velocity and height over a period of 2 years[10]. We now report the changes in bone density and metabolism in severe growth-retarded children with systemic and nonsystemic polyarticular JIA receiving glucocorticoids during treatment with GH for 4 years.

MATERIALS AND METHODS

Patient population and study protocol. Eleven prepubertal children with severe systemic or nonsystemic polyarticular JIA and growth retardation were enrolled. They were part of a controlled study on efficacy and safety of GH. The study has been described in detail[10]. Patients had diagnosis of JIA according to the International League of Associations for Rheumatology criteria (Durban criteria)[11]. All patients were Caucasian and clinically prepubertal according to Tanner[12] at inclusion. At onset of the disease mean age was 3.7 ± 1.4 years. Their mean age at inclusion was 10.3 years, with a range of 7.1 to 13.5 years. All had received daily glucocorticoids for a mean duration of 3.5 ± 0.8 years. Eight patients (4 girls/4 boys) entered puberty during the study. The mean duration of pubertal growth during the study period was 1.2 ± 1.0 years.

All children had a standard deviation score for height of –2.0 or below and/or a height velocity below the 25th percentile during the year before the beginning of GH treatment. Exclusion criteria were endocrinopathy or other metabolic or congenital disorders, renal failure, nephrotic syndrome, diabetes, heart failure, and previous treatment with GH.

Patients had been treated with glucocorticoids in a relatively stable dose for more than 6 months before inclusion and continued with glucocorticoid treatment during the study. Several types of glucocorticoids were used and converted to prednisolone-equivalent doses expressed in mg/kg body weight per day. Regular drug therapy was modified as necessary by the disease state, including nonsteroidal antiinflammatory drugs, slow acting antiinflammatory agents, methotrexate, or cyclosporin A.

In all children anthropometric measurements were obtained at 3 month intervals. Height was measured in a standing position, using a digital telescopic wall-mounted stadiometer (Ulmer Stadiometer, Prof. E. Heinze, University Children's Hospital, Ulm, Germany). Weight was determined to the nearest of 0.1 kg using an electronic scale (SECA 753 E, Vogel & Halke, Hamburg, Germany). Radiographs of the hand were obtained at approximately 12-month intervals. Bone age was determined by the Greulich-Pyle method[13]. In each patient, joint involvement was assessed clinically by the same experienced rheumatologist, and puberty was assessed with Tanner scores by the same experienced endocrinologist[12].

All patients received daily GH in a dose of 0.036 to 0.047 mg/kg bodyweight. Growth hormone was supplied by Pharmacia (Erlangen, Germany). The study protocol was approved by the ethics committee of Ludwig-Maximilians University. Written informed consent was obtained from the parents and oral or written consent from the children.

Laboratory assessment. Every 3 months blood samples were taken for measurement of hemoglobin, white and platelet cell count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatinine, fasting glucose, glycosylated hemoglobin, cholesterol, albumin, calcium, phosphate, and alkaline phosphatase. Insulin-like growth factor-I (IGF-I) and IGFBP-3, thyroid hormones, C-terminal propeptide of type I collagen (CICP) and urinary deoxypyridinoline (DpD) were measured at least every 6 months. IGF-I was measured using an immunoenzymetric assay, Octeia® IGF-I (IDS, Boldon, UK), and IGFBP-3 was measured using a radioimmmunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA). For measurement of CICP we used an enzyme immunoassay (F. Metra Biosystems, Osnabrück, Germany), for alkaline phosphatase we used Monotest® (Roche Diagnostics, Mannheim, Germany), and for DpD we used an ELISA (Quidel, Metra Biosystems, San Diego, CA, USA). For measurement of 25-OH-vitamin D we used a radioimmunoassay (Nichols Institute Diagnostics, Paris, France) and for intact parathyroid hormone (iPTH) we used an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany).

BMD assessment. BMD was assessed in a supine position at the lumbar vertebrae (L1–L4) by DEXA (Hologic QDR-1000, Hologic Inc., Waltham, MA, USA; software version 4.47). The lower limbs were partially elevated to obtain optimal separation of the lumbar vertebrae thus decreasing physiologic lordosis of this region.

Bone mineral content (BMC) values were corrected by scanned vertebral surface and expressed as area BMD values. Area BMD and a z-score were determined every year for each child over a period of 4 years.

For conversion of aBMD (g/cm^2), as calculated by the manufacturer's software, to volumetric BMD (vBMD; g/cm^3) the estimation of vertebral volume was based on the method proposed by Kröger, *et al*[6], assuming a cylindric shape of the spine. The vBMD, or apparent BMD, was calculated as follows:

$$vBMD = aBMD \, [4/(\pi \times width)]$$

where width stands for mean width of vertebral body. Width and aBMD were provided by the DEXA software program.

The validity of this model was tested using *in vivo* volumetric data obtained from magnetic resonance imaging of lumbar vertebrae[14]. The coefficient of variance (CV) for short term reproducibility *in vivo* was 1.02% for lumbar spine. Quality assurance tests were run daily at the hospital. The scanners were calibrated according to the phantom instrument provided by the manufacturer. The radiation dose equivalent was 0.01–0.05 mSv per measurement.

Statistical assessment. Growth rates are presented as annualized growth velocities (cm/yr). Reference data were taken from the Zurich Longitudinal Growth Study consisting of Caucasian Swiss-German children[15]. BMD was measured at study start and in one-year intervals. Reference data for area and volumetric BMD were taken from unpublished data and published reports[6,16,17]. Data were expressed as mean ± SD or mean and range. For conversion into age-specific SD scores (SDS) we used the formula:

$$SDS = [(test\ result\ for\ a\ patient) - (age\text{-}specific\ mean\ in\ reference\ population)]/(age\text{-}specific\ SD\ in\ reference\ population)$$

Statistical analysis was performed using SPSS 10.1 (SPSS, Chicago, IL, USA). We used the nonparametric Wilcoxon and Friedmann tests to evaluate comparisons of the mean and used one-way and 2-way analysis of variance (ANOVA) with appropriate confidence intervals of 95% for repeated measurements, after evaluating the validity assumptions. Statistical significance was defined as $p < 0.05$, 2-sided. To evaluate the effect of covariance (age, bone age, height), we used a general univariate linear regression analysis. Pearson's product-moment correlation was used to determine r values.

RESULTS

Growth and biochemistry. Height was very low, with a mean of –3.1 ± 0.9 SD (Table 1). After 4 years of GH treatment the patients' mean height expressed as SD scores had increased significantly to –2.1 ± 1.2 ($p < 0.05$). There was no statistical difference in height increment between prepubertal and pubertal patients. The gain of height correlated inversely with the mean ESR throughout the study ($R^2 = 0.44$, $p < 0.05$), but not with mean CRP level and mean prednisolone-equivalent dose. Mean concentrations of CRP, ESR, and prednisolone-equivalent dose decreased over 4 years: CRP from 2.7 to 0.8 mg/dl ($p < 0.05$), ESR from 26.3 to 14.8 mm/h (NS), and prednisolone-equivalent from 0.18 to 0.11 mg/kg body weight (NS). There was no statistical difference in disease activity variables between prepubertal and pubertal children. Pretrial IGF-I and IGFBP-3 concentrations were low, but within the normal range for age. IGF-

Patient	Sex	Age, yrs	Bone Age, yrs	Height SD	Growth Velocity, cm/yr	BMC, g	BMD, g/cm^2	BMD Z-score
1	M	9.5	7	–3.9	1	14.61	0.527	–1.9
2	M	11.8	10	–2.4	3.4	23.40	0.663	–1.6
3	M	12.8	9.8	–2.5	4.1	21.47	0.625	–2.3
4	M	13.5	12	–2.3	4.5	25.92	0.673	–1.9
5	F	9.4	8	–2.0	2.6	14.48	0.56	–1.0
6	F	9.4	8	–2.4	4	17.13	0.519	–1.9
7	F	8.3	6.5	–3.6	3.6	10.96	0.462	–2.4
8	F	10.9	9.5	–2.6	2.9	19.58	0.618	–2.0
9	F	8.5	6.5	–3.6	2	8.89	0.409	–2.6
10	F	7.1	6	–3.4	3.8	14.87	0.55	–0.3
11	F	12.6	11	–5	0.5	16.57	0.52	–3.2
Mean	4M/7F	10.3	8.6	–3.1	2.9	17.10	0.56	–2.04

I and IGFBP-3 increased significantly compared to baseline and remained significantly higher during GH treatment (Figure 1). Fasting glucose, HbA1c, cholesterol, electrolytes, and thyroid stimulating hormone (TSH) remained unchanged throughout the study in all patients.

BMD measures. At study start, mean values of aBMD and vBMD were significantly lower than those of the healthy reference population (Table 1). Mean aBMD at study start was 0.557 g/cm^2, or –2.04 ± 0.8 SD. After 4 years of GH treatment aBMD increased to 0.625 g/cm^2, a mean z-score of –1.8 ± 0.9. Considering vBMD, values increased from 0.198 g/cm^3 to 0.232 g/cm^3 (p < 0.03). Expressed as SD, there was a slight increase from –2.97 ± 0.81 to –2.83 ± 0.67 SD. Mean bone age retardation of the patients was 1.7 years. After 4 years of GH treatment the bone age was still delayed by a mean of 2 years. vBMD related to bone age showed an increase from –2.53 ± 0.85 to –2.41 ± 0.79 SD (Figure 2,
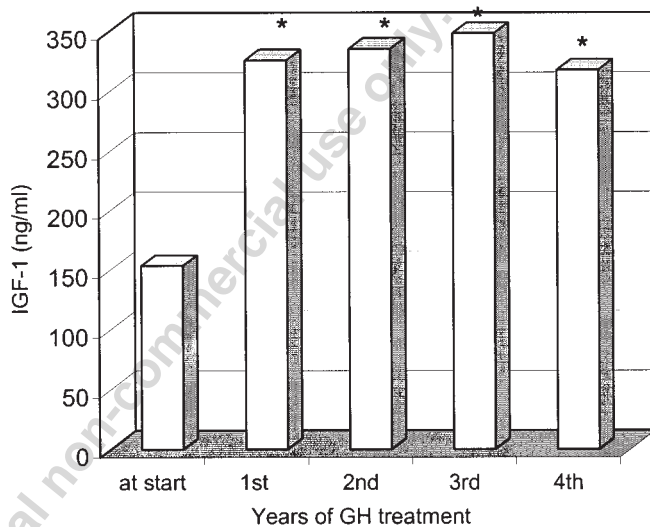

Figure 1. IGF-I concentrations at study start and during growth hormone treatment over 4 years; effect of growth hormone treatment on mean IGF-I concentrations. *Significant compared with pretreatment values, p < 0.01.

Table 2). Dividing the group into patients who remained prepubertal (n = 3) and those who entered puberty (n = 8) within the study period, prepubertal children lost vBMD z-score values for chronological age from –1.7 ± 1.3 to –2.1 ± 1.4, whereas pubertal children showed an increase of z-scores from –2.0 ± 0.6 to –1.6 ± 0.8 (NS). Expressing vBMD as percentage increase per year, prepubertal children had a mean increase of 2.4%, with pubertal boys 4.0% and pubertal girls of 5.9%. Comparing these values with normative data obtained by Kröger, *et al*[18], the relative increase in vBMD in the prepubertal and pubertal children was within normal limits. A single male patient (Table 1, Patient 2) did not show an increase in bone density due to severe disease activity and immobilization. He developed hip problems and has been wheelchair-bound for the last 2 years.

The duration of puberty within the observation period positively influenced the increase of aBMD and vBMD (R^2 = 0.64, p < 0.01, and R^2 = 0.61, p < 0.01, respectively). Interestingly, this was not the case for height gain. The increase in vBMD correlated significantly with mean values of IGF-I (R^2 = 0.38, p < 0.05), IGFBP-3 (R^2 = 0.41, p < 0.05), and gain of height (R^2 = 0.21, p < 0.05). There was no statistically significant influence of CRP, ESR, and prednisolone-equivalent dose on change of vBMD after 4 years. During the study, no fractures were observed in any patient.

Bone metabolism. Biochemical markers of bone formation, like alkaline phosphatase and CICP, and markers of bone resorption, like DpD, increased significantly during treatment (p < 0.05), indicating a higher bone turnover (Table 3). This was partially due to puberty. The increase of mean CICP, alkaline phosphatase, and DpD concentrations correlated significantly with the increase of mean vBMD levels after 4 years (p < 0.01). All study subjects had variable but normal serum and urinary calcium and phosphate levels at study start and throughout the study period of 4 years. Both iPTH and vitamin D were within normal limits throughout the study. There was a significant increase (p < 0.05) in iPTH levels after 4 years. There was no correlation between
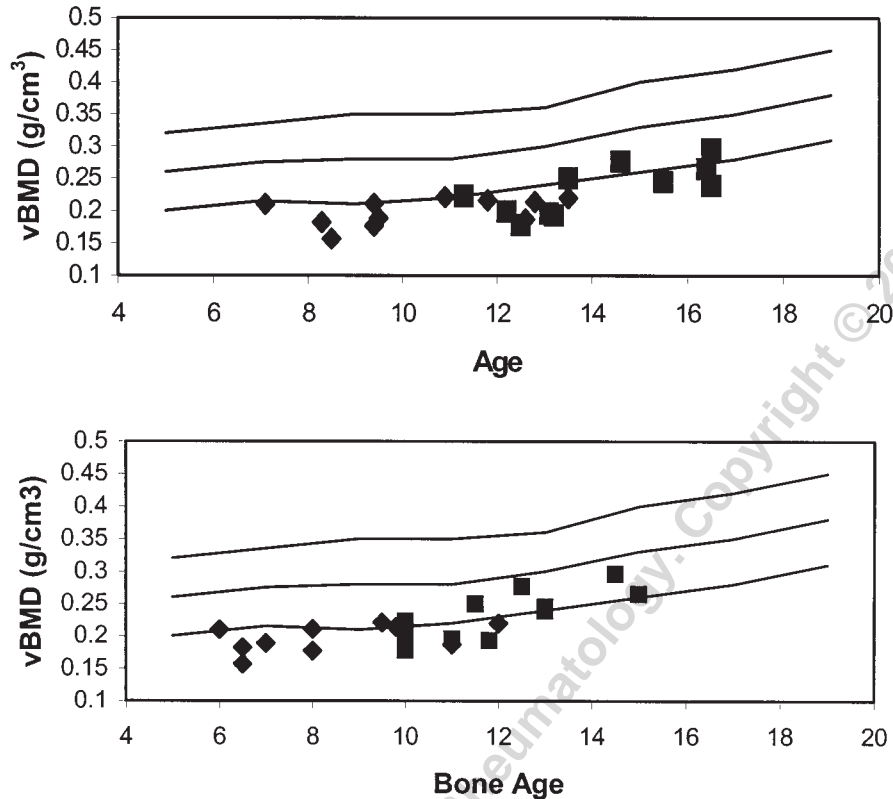
Figure 2. vBMD values at study start (◆) and after 4 years (■) in relation to chronological age (upper panel) and bone age (lower panel): 5th, 50th, and 95th percentiles according to the normative data[30].

markers of bone metabolism (CICP and alkaline phosphatase) and markers of disease activity (CRP and ESR).

DISCUSSION

The deleterious effects of glucocorticoids on height, bone mass, and fracture rate in general and in patients with RA are well known[19]. New technologies to estimate bone mass have shown that even relatively low doses of glucocorticoids have a negative effect on bone[20]. Not only glucocorticoids have to be taken into account — disease activity *per se* can cause bone loss.

We describe the effect of GH on BMD and bone metab-

Table 2. Changes in areal and volumetric BMD SD scores related to age, bone age, and Tanner stage (mean ± SD).

Bone Density	aBMD/Age	aBMD/Bone Age	vBMD/Age	vBMD/Bone Age
At start	−2.04 ± 0.8	−1.76 ± 0.7	−2.97 ± 0.81	−2.53 ± 0.85
After 4 years	−1.80 ± 0.9	−1.48 ± 0.8	−2.83 ± 0.67	−2.41 ± 0.79
p	NS	< 0.05	NS	NS

Table 3. Effect of growth hormone therapy for 4 years on variables of bone formation and resorption (mean ± SD).

Bone Metabolism	AP, U/l	CICP, µg/l	DpD/Creat, nmol/mmol	25-OH-Vit D_3, nmol/l	iPTH, pg/ml
Normative data	345 ± 105	330 ± 130	42.6 ± 10.1	175 ± 60	18 ± 6
Pretreatment values	175.2 ± 59	195.8 ± 71	13.3 ± 4.1	88.8 ± 49	15.4 ± 9
After 4 years	349.4 ± 128	379.7 ± 212	23.8 ± 8.4	95.2 ± 32	23.7 ± 7
p	< 0.05	< 0.05	< 0.05	NS	< 0.05

AP: alkaline phosphatase; CICP: C-terminal propeptide of type I collagen; DpD: deoxypyridinoline; Creat: creatinine; iPTH: intact parathyroid hormone.

olism in children with JIA treated with GH for 4 years because of severe growth retardation. As previously reported, modest but significantly greater linear growth was observed compared to an untreated control group with JIA over 2 and 4 years[10,21]. Since our study population consisted of growth-retarded children it is essential to adjust BMD for bone size. Katzmann, et al[22] found that in growing children 99% of the change in total body BMC and 50% of the change in lumbar spine BMC was caused by bone expansion rather than an increase in BMC per unit volume, emphasizing the importance of converting areal BMD to volumetric BMD.

Our major interest was the study of longitudinal bone density development in children with JIA. Children with JCA have a BMC decreased by 6–10% in comparison to sex and age matched healthy controls of the same height and weight[7]. Both the reduced bone mass and the reduced growth velocity seem to be related to the disease activity and glucocorticoid treatment. According to a study by Zak, et al[23] in adults, aBMD was most reduced in patients with more active disease, systemic glucocorticoid treatment, and the polyarticular form of JCA. In our small study population there was no correlation of bone density variables with disease activity or with glucocorticoid dose.

The percentage of vBMD increase was modest and within normal ranges for age and bone age. Even during puberty the percentage of increase was comparable to healthy controls at the same stage of puberty. The increase in BMD was not as dramatic as reported by Saggese, et al[24] in GH-deficient but otherwise healthy patients during GH treatment. However, apart from GH treatment, our patients with JIA are not comparable with GH-deficient patients[4]. Stabilization and avoidance of further bone loss during GH treatment could be interpreted as a beneficial effect in these patients.

The delay in puberty may contribute to the observation that normal peak bone mass is not achieved. According to Pepmueller, et al[25], BMD, BMC, and vBMD in JRA were reduced in pre- and postpubertal children, and declined further with age. Hopp, et al[7] described a lack of pubertal bone mass increment in pubertal girls with JCA in contrast to healthy girls in puberty. Pubertal bone accumulation greatly contributes to peak bone mass. Any impairment of bone formation during this critical period is of great importance and may be irreversible later in life. Bonjour, et al[26] observed that bone mass accumulation is only slightly influenced by the timing of puberty. Prepubertal and pubertal patients in our study showed an increase in bone density during 4 years with GH treatment that was comparable with healthy children. Possibly this beneficial effect on bone was due to GH.

Since GH has anabolic effects on bone, Saggese, et al[24] thought GH deficiency to be the major cause of osteopenia in GH-deficient children. During GH treatment of children with GH deficiency, Boot, et al[27] found a significant increase in lumbar spine BMD after adjustment for size. Patients with JIA are not GH-deficient, but some GH resistance may explain the increase in growth and vBMD we found in our patients[28]. There was a significant correlation of height gain and growth velocity with the increase in vBMD over 4 years. Since height and weight are the best indicators of bone accretion in healthy children, it is not surprising that a similar and significant trend was observed in our children with JIA during treatment with GH.

GH has both direct and indirect actions on bone. The anabolic effect of GH is based on stimulation of osteoblast number and function and on production of various bone matrix factors[29]. Part of the effects of GH are mediated through IGF-I. It is well known that glucocorticoids lower systemic and local IGF-I levels and responses, reduce osteoblastic activity, inhibit collagen synthesis, and increase collagen degradation[30]. Synthesis of type I collagen is impaired by glucocorticoids, but stimulated by GH[31]. In our patients an increase in alkaline phosphatase and CICP plasma concentrations in response to GH treatment was associated with an increase in IGF-I plasma levels. Serum and urinary calcium levels were variable, and did not change consistently throughout the study. This is in contrast to experiences with GH-deficient children[24]. A possible explanation could be the disease itself[4], or a consequence of depletion of calcium stores[5]. Markers of osteoclast activity (DpD) were diminished in patients with JIA, but decreased bone formation was the primary factor[30]. In our study population IGF-I levels and markers of bone turnover increased significantly and remained elevated within normal levels throughout the study. Bone formation stimulated by GH must outweigh bone resorption, since there was a net increase of BMD. In the study by Trivedi, et al[32] CICP and bone alkaline phosphatase were related to linear growth velocity and disease activity in juvenile arthritis. The correlation of laboratory markers of disease severity with depression of bone formation suggested that there was a direct effect of disease activity on bone turnover. Such an association would most likely be modulated by cytokines[25]. The number of patients in our study was too small to show a significant association between disease activity and bone formation and resorption, but a trend was obvious.

In conclusion, GH treatment resulted in a modest increase in height, height velocity, aBMD, vBMD, and indicators of bone metabolism. Stabilization of BMD and prevention of further bone loss despite ongoing glucocorticoid treatment may be considered a beneficial effect of GH treatment. In part, the decrease in disease activity and puberty may have played complementary roles in our study. Data on peak bone mass development during GH treatment in patients with JIA undergoing glucocorticoid therapy are lacking. Final height and postpubertal BMD values are needed to correctly interpret the effect of GH on bone in

patients with JIA. Thus, longterm studies are necessary to confirm these preliminary data, and to document whether GH can offset the osteopenia caused by the combination of disease activity and glucocorticoid therapy.

ACKNOWLEDGMENT

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