0021-972X/07/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 92(3):932–937

doi: 10.1210/jc.2006-0385

Growth Hormone Therapy Improves Bone Mineral Density in Children with Cerebral Palsy: A Preliminary Pilot Study

Omar Ali, Melanie Shim, Eileen Fowler, Marcia Greenberg, Donna Perkins, William Oppenheim, and Pinchas Cohen

David Geffen School of Medicine at University of California, Los Angeles (E.F., M.G., D.P., W.O., P.C.), Los Angeles, California 90095; Southern California Permanente Medical Group (M.S.), Los Angeles, California 90034; and Medical College of Wisconsin (O.A.), Milwaukee, Wisconsin 53226

Context: Cerebral palsy is associated with osteopenia, increased fracture risk, short stature, and decreased muscle mass, whereas GH therapy is associated with increased bone mineral density (BMD) and linear growth and improvement in body composition.

Objective: We conducted a pilot study to evaluate the effect of 18 months of GH therapy on spinal BMD, linear growth, biochemical markers, and functional measures in children with cerebral palsy.

Design and Setting: The study was a randomized control trial, conducted from 2002–2005 at the University of California, Los Angeles, Orthopedic Hospital's Center for Cerebral Palsy.

Patients: Patients included 12 males with cerebral palsy, ages 4.5–15.4 yr.

Intervention: We compared 18 months of GH (50 μg daily) *vs.* no treatment.

Primary Outcome Measures: Spinal BMD (dual-energy x-ray absorptiometry scan), height, growth factors, and bone markers were assessed.

Results: Ten subjects (five in each group) completed the study. Pre- and post-average height z-scores were -1.47 ± 0.23 and 0.8 ± 0.2 (GH-treated group) *vs.* -1.35 ± 1.26 and -1.36 ± 1.27 (control group) (Δ SD score, 0.67 *vs.* -0.01; $P = 0.01$). Average change in spinal BMD z-score (Δ SD score corrected for height) was 1.169 ± 0.614 *vs.* 0.24 ± 0.25 in the treated and control groups, respectively ($P = 0.03$). Osteocalcin, IGF-I, and IGF-binding protein 3 levels increased during GH therapy. There was no change in quality of life scores as measured by the Pediatric Orthopedic Disability Inventory.

Conclusions: This small pilot study suggests that 18 months of GH therapy is associated with statistically significant improvement in spinal BMD and linear growth. **(*J Clin Endocrinol Metab* 92: 932–937, 2007)**

CEREBRAL PALSY (CP) is a static encephalopathy that may be defined as a nonprogressive disorder of posture and movement resulting from a defect or lesion of the developing brain. It is a common disorder, with an estimated prevalence of two in 1000 population (1). Children with CP are at increased risk for growth failure (2), osteopenia (3–5), small, thin bones (6), and decreased muscle mass (7). There is an increased risk of fractures, including spontaneous fractures, and these are a cause of significant morbidity (8–10). Data correlating the degree of osteopenia with fracture risk are not available in children, but in adults each one SD decrease in bone mineral density (BMD) is associated with a 2.4- to 3.0-fold increase in the age-adjusted risk of hip fracture (11).

Factors that contribute to impaired bone health in these children include immobilization, muscle weakness, malnutrition, and the use of anticonvulsant drugs. These children may have an increased incidence of GH deficiency, and their IGF-I and IGF-binding protein 3 (IGFBP-3) levels tend to be lower than in age-matched controls (12, 13). It is possible that such deficiencies play a role in impaired bone health in some patients with CP, but this question has not yet been systematically studied, and this possibility remains speculative at this time. Still, there is abundant evidence that the GH-IGF axis plays an important role in bone growth. For example, GH and IGF-I are key regulators of bone-cell function (14); IGF-I has potent stimulatory effects on the synthesis of bone-specific proteins and osteoblastic proliferation in cell cultures (15); congenic mice with low IGF-I levels have decreased BMD (16), and circulating IGF-I and IGFBP-3 correlate positively with BMD in humans (17). There is also abundant evidence that GH therapy leads to an increase in BMD. This has been reported in children with GH deficiency (18, 19), idiopathic short stature (20), and a history of being small for gestation age (21). GH has also been considered as a putative anabolic agent for the treatment of osteoporosis in adults, irrespective of the cause of osteopenia (22). As an initial test of the hypothesis that GH treatment can increase BMD in children with CP, we carried out a small, preliminary pilot study.

Subjects and Methods

Subjects were recruited from the University of California, Los Angeles (UCLA)/Orthopedic Hospital's Center for Cerebral Palsy. The

First Published Online December 19, 2006

Abbreviations: BCE, Bone collagen equivalents; BMD, bone mineral density; BMI, body mass index; CP, cerebral palsy; DXA, dual-energy x-ray absorptiometry; GMFCS, Gross Motor Functional Classification System; IGFBP-3, IGF-binding protein 3; PODCI, Pediatric Orthopedic Disability Inventory.

JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.

study design was approved by the UCLA Institutional Review Board. We screened 30 children with CP for osteopenia using dual-energy x-ray absorptiometry (DXA). Inclusion criteria were age 3–18 yr, spastic CP, and spinal BMD less than −1.0 SD for age. Children with prior history of treatment for osteoporosis, other known bone disease, prior use of GH, active malignancy or diabetes mellitus, weight less than 85% of ideal body weight, triceps skin-fold measurement less than the 5th percentile for age, or albumin less than 3.0 g/dl were excluded. Twelve children meeting these criteria consented to participate in the study. Patients were randomized into two groups using a computerized random number generator.

All patients underwent a baseline physical examination, including height measurement on a wall-mounted stadiometer (Holtain Ltd., Crymych, UK) or length measurement using a recumbent length board (Ellard Instrumentation Ltd., Seattle, WA) depending on their ability to stand. Each patient was measured twice, and the average of the two measurements was recorded. Patients were measured by the same clinician at each visit throughout the study to ensure that a consistent measuring technique was used.

Spinal BMD was measured by DXA scan (Hologic QDR 4500 A, Hologic Corp., Bedford, MA), and the same machine, operated by the same operator, was used for all patients. For children over the age of 9 yr, the SD score (SDS) was calculated using the online BMD applet developed at Stanford University by Bachrach *et al.* (http://www-stat-class.stanford.edu/pediatric-bones/) (23). For children under the age of 9 yr, the standards supplied by the Hologic Corp. were used to calculate the SDS (24).

Parents were interviewed by a dietitian to assess adequacy of oral intake. A 3-d diet record was evaluated by a dietitian, and recommendations were made to optimize nutritional intake as needed. Recommendations were primarily focused on ensuring that the dietary reference intakes for calcium and vitamin D were met. Nutritional status was also assessed by calculating the body mass index (BMI) and measuring triceps skin-fold thickness and serum albumin.

Health-related quality of life was assessed using the Pediatric Orthopedic Disability Inventory (PODCI version 2.0, May 1997) via a questionnaire completed by parents (25).

Serum IGF-I and IGFBP-3 levels were measured using standard assays at Esoterix Laboratories, Calabasas, CA. Serum calcium, phosphorous, PTH, 25-OH vitamin D, osteocalcin, and bone-specific alkaline phosphatase as well as urinary N-telopeptide were measured using standard methods in the UCLA Medical Center Laboratory.

Patients randomized to the GH group were trained in the use of the Nutropin pen device and started on treatment at a dose of 50 μg/kg·d of Nutropin AQ (Genentech, San Francisco, CA). All patients also received a children's multivitamin and mineral supplement (Centrum Kids Complete; Whitehall-Robins Healthcare, Madison, NJ), one tablet daily, containing 400 IU vitamin D. A calcium supplement containing 500 mg elemental calcium (Calci-Mix; R&D Laboratories, Marina del Ray, CA) was prescribed if dietary assessment indicated that calcium intake from foods did not meet recommended daily requirements.

Patients were examined at baseline and at 3, 6, 12, and 18 months after the first visit. At each visit, the patient was examined by a physician and auxological parameters (height or length, weight, and BMI) were recorded. The patient's diet was reviewed by a dietitian to determine whether any significant changes had occurred. Blood was drawn for IGF-I, IGFBP-3, osteocalcin, and bone-specific alkaline phosphatase at each visit, whereas urine was collected for measurement of urinary N-telopeptide. Finally, at the 18-month visit, a follow-up DXA was obtained, and the parents/guardians of subjects completed the PODCI.

Statistical methods and analysis of data

We initially calculated BMD SDS based on the patient's chronological age to assess suitability of the patients for the study. But to eliminate the influence of excess height gain in the GH treatment group on the DXA result (see *Discussion*), we then calculated BMD SDS based on the height age rather than the chronological age. That is, we calculated the height age of each patient (age at which the patient's height would be the 50th percentile on the standard National Center for Health Statistics growth charts) and calculated BMD SDS based on height age instead of chronological age. These height-age-based SDS were then used to compare pre- and posttreatment results.

SDS were calculated for height and BMI using the published National Health and Nutrition Examination Survey standards (26). SDS were also calculated for the IGF-I and IGFBP-3 levels based on the age- and sex-matched standards supplied by Esoterix Laboratories.

The data are presented as means ± SD. Differences between the treatment and control groups were assessed by the two-tailed Student's *t* test comparing average measurements at each time point and by ANOVA to compare all measurements in one group with all measurements in the other. *P* values were calculated using a computerized statistical program (InStat version 2.0 and GraphPad prism 4) with an α of $P < 0.05$.

Results

Twelve subjects ranging in age from 5–15 yr were enrolled in the study. Two patients did not get final DXA scans and were not included in the analysis of BMD data. These included one patient in the treated group who underwent orthopedic surgery for scoliosis and one patient in the control group that failed to get a final DXA scan. All subjects had the spastic form of CP. Severity of mobility impairment was assessed using the Gross Motor Functional Classification System (GMFCS), where level I represents the highest level of mobility and level V represents the lowest (27). Both groups were comparable in age, height, BMI, and PODCI scores. Measures of calcium and vitamin D status were also similar in both groups (Table 1). The baseline spinal BMD z-score was similar in both groups based on chronological age. When the z-score was calculated based on height age, the initial BMD z-score changed to a smaller value because these children were generally shorter then average, so their height age was less than their chronological age. The control group mean z-score based on height age was −0.78, whereas the z-score of the treatment group was now −1.7 ($P = 0.11$). We then used the height-age-based z-score for all subsequent calculations.

The distribution of CP and the GMFCS level of each subject are listed in Table 2. Pubertal status was similar in both groups, and during the study, two patients went through puberty in each group. One patient in the control group experienced worsening of scoliosis during the study. There was no apparent correlation between progression through puberty and change in BMD SDS in either group, nor was there any correlation between BMD z-score and functional status.

TABLE 1. Baseline characteristics of GH-treated and control CP patients

	Controls (n = 6)	GH treatment (n = 6)
Age (yr)	10.15 ± 3.4	10.1 ± 4.7
Sex	Male	Male
Height (SDS)	−1.35 ± 1.36	−1.47 ± 0.25
BMI (SDS)	−0.5 ± 1.8	−0.7 ± 0.9
Spinal BMD z-score (chronological age)	−2.24 ± 0.65	−2.5 ± 0.33
Spinal BMD z-score (height age)	−0.78 ± 0.71	−1.7 ± 0.6
PODCI score	53.37 ± 27	62.7 ± 32
Calcium (mg/dl)	9.6 ± 0.5	9.8 ± 0.3
Phosphorus (mg/dl)	5 ± 1.1	4.5 ± 0.4
PTH (pg/ml)	47.5 ± 30	30 ± 14
25-OH Vitamin D (ng/ml)	32.6 ± 17.5	43.8 ± 15
Bone-specific alkaline phosphatase (μg/liter)	74.8 ± 18	68.8 ± 28

TABLE 2. Individual patient characteristics

Patient no.	Age at entry (yr)	Baseline BMD	ΔBMD SDS	Type of CP	GMF CS level	Pubertal status, entry[a]	Pubertal status, final[a]	Scoliosis baseline[b]	Scoliosis final[b]
1	11.4	−1.78	−0.14	Spastic quadriplegia	V	1	2	1	1
2	7.7	−1.4	0.37	Spastic triplegia	V	1	1	0	0
3	13.2	−0.3	0.15	Spastic diplegia	IV	3	5	1	2
4	14.8	−0.838	0.127	Spastic diplegia	II	3	5	1	1
5	7.5	0.4	0.7	Spastic hemiplegia	II	1	1	0	0
6	14.9	−1.08	0.384	Spastic hemiplegia	I	3	5	1	1
7	4.5	−1.5	2.24	Spastic diplegia	III	1	1	1	1
8	6.2	−1.45	0.61	Spastic quadriplegia	V	1	1	1	1
9	6.6	−1.53	1.03	Spastic hemiplegia	I	1	1	0	0
10	11.8	−2.98	1.58	Spastic triplegia	II	2	4	0	0

Patients 1–5 were in the control group and patients 6–10 in the treatment group. GMFCS levels are: I, walks without restrictions; II, walks without assistive devices, limitation walking in the community; III, walks with assistive mobility devices, limitation walking in the community; IV, primarily uses wheelchair for mobility, may walk short distances; and V, self-mobility is severely limited. BMD SDS are based on height age.

[a] Genital Tanner stage.

[b] 0, No scoliosis; 1, mild; 2, moderate.

Auxology

During the course of the study, the average height SDS of the untreated group decreased from −1.35 ± 1.26 to −1.36 ± 1.27. In the GH-treated group, the average height SDS increased from −1.47 ± 0.23 to −0.8 ± 0.2 after 18 months of GH therapy. Thus the change in height SDS (ΔSDS) was 0.67 in the treated group *vs.* −0.01 in the untreated group (Fig. 1; $P = 0.013$).

Growth factors

Serum IGF-I SDS decreased in the untreated group from a baseline of −0.82 ± 0.6 to −1.13 ± 0.61 after 18 months. In contrast, in the treated group, the IGF-I SDS increased from −0.75 ± 0.9 to 0.46 ± 0.69 after 18 months of GH therapy (Fig. 2A, ΔSDS 1.21 *vs.* −0.3, $P = 0.08$). Similarly, the IGFBP-3 SDS declined from −0.71 ± 1.4 to −0.92 ± 0.76 in the untreated group but increased from −0.25 ± 1.24 to 0.66 ± 0.7 in the treated group (Fig. 2B, ΔSDS 0.91 *vs.* −0.21), but this difference was not statistically significant, with $P = 0.3$.

Bone markers

At baseline, the urinary N-telopeptide (a marker of bone resorption) was 322 ± 33 nmol bone collagen equivalents (BCE)/mmol creatinine in the control group *vs.* 426 ± 65 nmol BCE/mmol creatinine in the treated group ($P = 0.017$). The values at 3, 6, 12, and 18 months are shown in Fig. 3A and indicate that the N-telopeptide increased in the treated group but not in the control group, with the difference approaching significance at 6 months and being significantly greater at 12 months. But by 18 months, the treated group

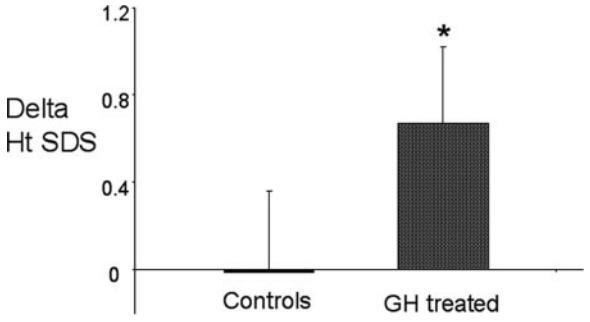

FIG. 1. Effect of GH therapy on height SDS in all patients: the change in height SDS (Δ Ht SDS) over 18 months of treatments with GH (n = 5) or control (n = 5). *, $P = 0.01$.

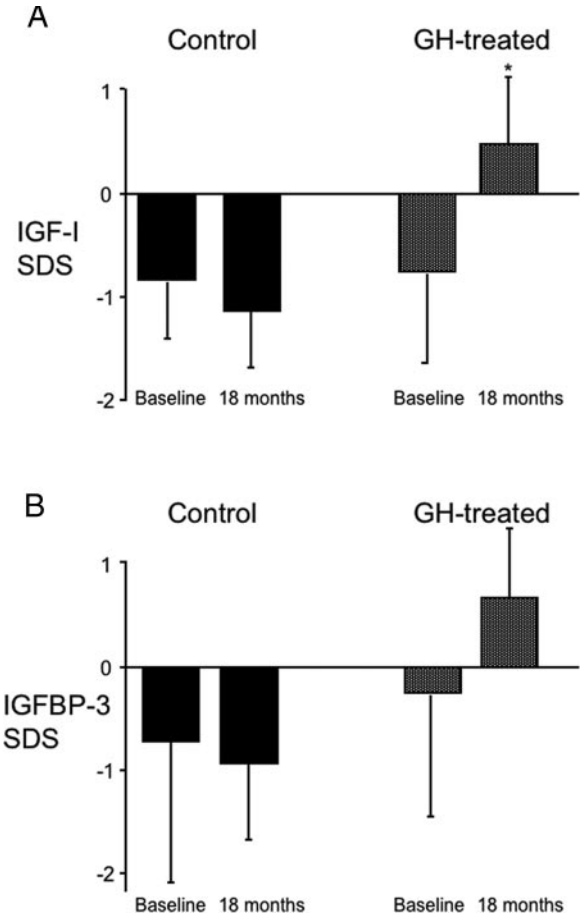

FIG. 2. Effect of GH therapy on IGF-I and IGFBP-3 in all patients. A, Effect of GH therapy on IGF-I SDS. IGF-I SDS values are shown before and after 18 months of GH treatment and in untreated controls over the same time period. *, $P < 0.001$. B, Effect of GH therapy on the IGFBP-3 SDS. IGFBP-3 SDS before and after 18 months of treatment.

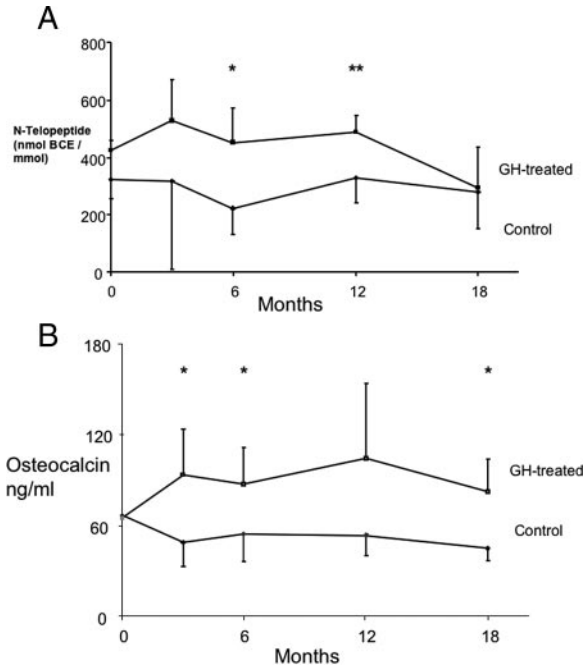

FIG. 3. Effects of GH therapy on bone markers in all patients. A, Effect of GH therapy on urinary N-telopeptide. Shown are the average urinary N-telopeptide levels at 0, 3, 6, 12, and 18 months. The two groups' means difference approached significance at 6 months (*, $P = 0.06$) and were statistically different at 12 months (**, $P = 0.006$). B, Effect of GH therapy on serum osteocalcin level. Shown are the average serum osteocalcin levels at 0, 3, 6, 12, and 18 months. The two group means were similar at baseline. The GH-treated group's mean osteocalcin rose higher and remained elevated at each time point. The difference between the two groups was statistically significant at 3, 6, and 18 months (*, $P < 0.05$).

mean had declined to 295 ± 92 nmol BCE/mmol creatinine, which is not significantly different from the control group mean of 279 ± 140 nmol BCE/mmol creatinine.

Changes in serum osteocalcin (bone GLA protein), a marker of bone formation, are shown in Fig. 3B. The two groups were comparable at baseline (controls 66.9 ± 27 ng/ml *vs.* treated 65 ± 23.5 ng/ml). There was no significant change in the control group, but in the treated group, the serum osteocalcin increased at 3 months and remained elevated at 6, 12, and 18 months, with the difference between the two groups statistically significant at 3, 6, and 18 months. Calcium, phosphorous, bone-specific alkaline phosphatase, and 25-OH vitamin D levels remained within the normal range throughout the study and were not significantly different between the two groups at any point (data not shown).

Bone density

Average spinal BMD SDS (calculated by height age) in the untreated group was −0.78 ± 0.71 at baseline and was not statistically different at 18 months at −0.54 ± 0.9 (ΔBMD SDS = 0.24 ± 0.25). In the GH-treated group, the spinal BMD SDS (calculated by height age) increased from −1.7 ± 0.6 to −0.54 ± 0.64 after 18 months of therapy (ΔBMD SDS = 1.169 ± 0.614). The change in the BMD SDS was higher in the treated group *vs.* the controls ($P = 0.03$, Fig. 4).

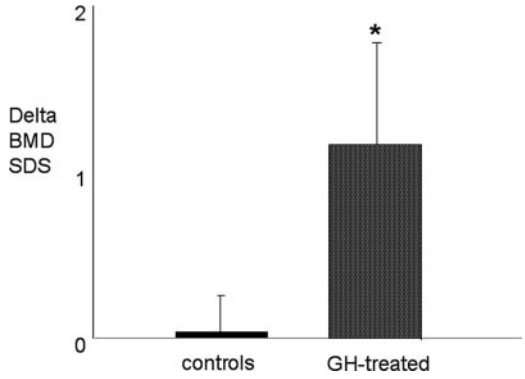

FIG. 4. Effect of GH therapy on BMD SDS (based on height age) in CP patients. Shown are ΔBMD SDS in the treated and control groups. *, $P = 0.03$.

Discussion

Osteopenia is a common finding in children with CP and is associated with an increase in the risk of fractures, including spontaneous fractures (8–10). In addition, GH therapy, in a variety of settings, is associated with increase in BMD (18–21). Thus, it is not surprising that in our small pilot study, 18 months of GH therapy led to an increase in spinal BMD. As expected, GH therapy also increased linear growth, IGF-I, and IGFBP-3 levels in our patients.

Patients were initially enrolled in the study based on the BMD SDS derived from their chronological age; *i.e.* if the BMD SDS was greater than −1 based on the patient's age-matched norms, he was considered a candidate for the study. Once enrolled, we calculated their BMD SDS based on height age and used these scores in all subsequent calculations. This was done because one limitation of areal BMD determination is that it is a two-dimensional picture of a three-dimensional structure, and apparent BMD increases with age simply due to growth in size, even when actual bone density has not changed. Thus, a group of patients that exhibits greater increase in height (as our GH-treated patients did) will also show a greater increase in apparent BMD. To exclude this effect of height increase, we used height age instead of chronological age to calculate z-scores in our patients.

There are several limitations to our study. The most important is that the number of subjects is very small and the age range is very broad. In this heterogeneous population, the possibility of confounding factors cannot be excluded, and the study lacks the power to detect small but potentially significant differences between the two groups. On the other hand, the fact that a statistically significant improvement in the BMD was seen in such a small sample indicates that the treatment effect may be real. We found that there was a uniform increase in BMD in the treated group, but no such consistent trend is seen in the control group (Table 2) This increases the likelihood that the observed increase is real and reproducible. Pubertal status is a potential confounder in such a study, but fortunately, the same number of patients went through puberty in each of the randomly selected groups (two patients in each group), and there was no correlation between pubertal development and BMD or ΔBMD. Ambulatory status is another potential confounder in this

study, but contrary to expectations, there was no correlation between ambulatory status and BMD in either group.

Also, osteopenia is not the only factor that determines fracture risk in children. The risk of fracture is determined by several factors, including the geometry, quality, and material properties of the bone in question. Thus, we are unable to prove that the observed increase in BMD necessarily leads to a decrease in fracture risk. A much larger study of greater duration will be needed to show that GH therapy actually decreases fracture risk in children with CP.

There is no ideal method of measuring bone density in children, and each available method has its advantages and disadvantages. It may be that DXA scanning is not the best method to monitor BMD and change in BMD in growing children. But DXA scans are easy to perform, have low cost, involve minimal radiation exposure, and have more normative data available than other techniques, so DXA remains the most popular means of assessing BMD in children.

Finally, most spontaneous fractures occur in the periphery, and the correlation between spinal BMD and peripheral BMD is variable and has not been systematically studied in children with CP (28–30). It has also been reported that GH therapy affects BMD to different extents at different sites (31). On the other hand, the accuracy and precision of DXA scanning are greater in the posteroanterior spine than in the periphery (32), and more detailed normative data are available for this site, so we decided to limit our pilot study to an examination of spinal BMD.

It has previously been reported that GH therapy may lead to a transient decrease in BMD in the first 3–6 months, followed by a sustained increase with longer duration of therapy (33, 34). Because we did not measure BMD at 3, 6, or 12 months, we cannot exclude the possibility that there was an initial decrease in BMD in our patients. We did see an initial increase in urinary N-telopeptide (a marker of bone resorption), which returned to baseline by 18 months. At the same time, there was a sustained increase in osteocalcin (a maker of bone formation). Thus, it is possible that, as in previous studies, there was a transient decrease in BMD in our patients, followed by the increase seen at 18 months.

The dose of GH used in our study (50 μg/kg·d) is now commonly considered by many to be the standard of care in the treatment of several conditions where GH therapy is indicated but where classical GH deficiency may not be present (*e.g.* short for gestational age, Turner Syndrome, and idiopathic short stature). It is the default starting dose in several institutions, including ours, and has been published as such (35, 36).

There was no difference in the quality of life, as measured by PODCI scores, between the two groups after treatment (data not shown). It may be that our sample size was very small and did not have sufficient power to detect differences between the two groups, or it may be that 18 months of GH treatment does not lead to any significant improvement in health-related quality of life in patients with CP.

Conclusion

This is a very small initial pilot study, performed on a relatively heterogeneous population. Although it demonstrates that 18 months of GH therapy is associated with a statistically significant improvement in spinal BMD, the clinical significance of this finding is not known, and the possibility of confounding factors cannot be excluded. This study should, therefore, be regarded as preliminary, and its results need to be replicated in larger studies before GH therapy can be regarded as an option in children with CP.

Acknowledgments

Received February 21, 2006. Accepted December 8, 2006.

Address all correspondence and requests for reprints to: Pinchas Cohen, Division of Pediatric Endocrinology, Mattel Children's Hospital at UCLA, MDCC 22-315, 10833 Le Conte Avenue, Los Angeles, California 90095. E-mail: Hassy@mednet.ucla.edu.

This project was supported by the UCLA Clinical Research Center, the United Cerebral Palsy Research and Educational Foundation, and the Genentech Center for Clinical Research and Education (Grant 900-C02-GH).

Author Disclosure Summary: O.A., M.S., E.F., M.G., D.P., and W.O. have nothing to declare. P.C. consults for Novo Nordisk, has previously consulted for Eli Lilly and Serono, and received grant support (2002–2004) from Genentech.

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