

ORIGINAL ARTICLE

Long-Term, High-Dose Glucocorticoids and Bone Mineral Content in Childhood Glucocorticoid-Sensitive Nephrotic Syndrome

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ABSTRACT

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BACKGROUND

Glucocorticoids suppress bone formation, impair growth, and induce obesity. We determined the effects of long-term treatment with glucocorticoids on bone mineral content in children with glucocorticoid-sensitive nephrotic syndrome, a disorder with minimal known independent effects on bone.

METHODS

We performed dual-energy x-ray absorptiometry of the whole body and spine in 60 children and adolescents with the nephrotic syndrome and 195 control subjects. We used linear regression analysis of log-transformed values to compare the bone mineral content in patients with that in controls.

RESULTS

Patients had received an average of 23,000 mg of glucocorticoids and were shorter ($P=0.008$) and had a greater body-mass index ($P<0.001$) than controls. The bone mineral content of the spine, adjusted for bone area, age, sex, degree of maturation (Tanner stage), and race, did not differ significantly between patients and controls (ratio, 0.99; 95 percent confidence interval, 0.96 to 1.02; $P=0.51$). After adjustment for the z score for body-mass index, the bone mineral content of the spine was significantly lower in patients than in controls (0.96; 95 percent confidence interval, 0.92 to 0.99; $P=0.01$). Whole-body bone mineral content, adjusted for height, age, sex, degree of maturation, and race, was significantly higher in patients than in controls (ratio, 1.11; 95 percent confidence interval, 1.05 to 1.18; $P<0.001$); however, the addition of the z score for body-mass index to the model eliminated the association with the nephrotic syndrome (ratio, 0.99; 95 percent confidence interval, 0.94 to 1.03; $P=0.55$).

CONCLUSIONS

Intermittent treatment with high-dose glucocorticoids during growth does not appear to be associated with deficits in the bone mineral content of the spine or whole body relative to age, bone size, sex, and degree of maturation. Glucocorticoid-induced increases in body-mass index were associated with increased whole-body bone mineral content and maintenance of the bone mineral content of the spine.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS is caused by decreased bone formation and increased bone resorption.¹ Studies in adults have demonstrated that glucocorticoids cause rapid, dose-dependent bone loss and an increased risk of fracture.^{2,3} During childhood and adolescence, skeletal modeling results in sex- and maturation-specific increases in bone dimensions and density. Children may be especially vulnerable to the effects of glucocorticoids on bone formation, including a possible compromise in peak bone mass.

Decreased bone mineral density has been described in various pediatric disorders requiring glucocorticoid therapy, including juvenile rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.⁴ A population-based study reported an increased risk of fracture among children who required more than four courses of glucocorticoids.⁵ Although these studies demonstrated a correlation among glucocorticoids, bone deficits, and the risk of fracture, some of the detrimental effects on bone attributed to glucocorticoids may be due to the underlying inflammatory disease. For example, inflammatory cytokines have been implicated in bone resorption in patients with rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.⁶

In contrast to other conditions requiring long-term glucocorticoid therapy in childhood, glucocorticoid-sensitive nephrotic syndrome remits completely and quickly in response to glucocorticoids. Unfortunately, the nephrotic syndrome relapses at intervals in the majority of children after the dose of glucocorticoids is reduced or discontinued, resulting in protracted, repeated courses of glucocorticoids. The standard dose of prednisone for relapses is 2 mg per kilogram of body weight per day,⁷ far exceeding the daily dose of 5 mg considered to be a risk factor for glucocorticoid-induced osteoporosis in adults.² Although relapses of the nephrotic syndrome are associated with transient increases in cytokines and urinary losses of vitamin D, these abnormalities promptly resolve with glucocorticoid therapy and disease remission.⁸⁻¹⁰ Therefore, we selected glucocorticoid-sensitive nephrotic syndrome as a clinical model without substantial systemic inflammatory involvement to examine the effects of glucocorticoids on the growing skeleton. We determined the effects of long-term therapy with high-dose glucocorticoids on the bone mineral content of the lumbar spine and whole body

relative to bone size and body size in children and adolescents.

METHODS

STUDY SUBJECTS

The study subjects were enrolled from 1996 through 1999. Children and adolescents with glucocorticoid-sensitive nephrotic syndrome were identified through a systematic review of medical records at the Children's Hospital of Philadelphia and St. Christopher's Hospital for Children in Philadelphia. Patients fulfilling the diagnostic criteria for glucocorticoid-sensitive nephrotic syndrome (defined by a negative urine-dipstick test or one showing trace levels of protein within 8 weeks after the initiation of prednisone treatment)¹¹ were eligible, provided they had received glucocorticoids within 12 months before the study visit. Patients were excluded if they had renal insufficiency (defined by a glomerular filtration rate of less than 90 ml per minute per 1.73 m² of body-surface area)¹² or other conditions unrelated to the nephrotic syndrome that could affect growth or bone health. The minimal age at enrollment was four years, so that we could enroll subjects who were able to cooperate during dual-energy x-ray absorptiometry. Study visits were scheduled at least 14 days after a documented remission to ensure that edema had resolved. The absence of proteinuria and edema was documented at the time of the study visit.

Healthy control subjects were recruited from pediatric clinics and the surrounding community. Subjects with medical conditions potentially affecting growth and development were excluded.

The protocol was approved by the institutional review board of each hospital. Written informed consent was obtained from the parents or guardians of all subjects. Assent was obtained from children over seven years of age.

CHARACTERISTICS OF THE NEPHROTIC SYNDROME

The medical charts of all patients were reviewed to determine the date of diagnosis of glucocorticoid-sensitive nephrotic syndrome, the dates and numbers of relapses, and prior therapies. All doses of prednisone and methylprednisolone were documented and converted to prednisone equivalents. The total glucocorticoid exposure was summarized in terms of cumulative milligrams, milligrams per kilogram, and milligrams per kilogram per day.

ANTHROPOMETRY AND PUBERTAL ASSESSMENT

Height and weight were measured at the time of dual-energy x-ray absorptiometry with the use of a digital scale and a wall-mounted stadiometer, respectively. Pubertal status was determined by a physical examination and classified according to the method of Tanner.¹³ Age- and sex-specific standard-deviation scores (z scores) for height, weight, and body-mass index (the weight in kilograms divided by the square of the height in meters) were calculated with the use of national data.¹⁴ Obesity was defined as a body-mass index greater than the 95th percentile.¹⁵

DUAL ENERGY X-RAY ABSORPTIOMETRY

Dual-energy x-ray absorptiometry scans (QDR 2000, Hologic) of the whole body and lumbar spine (L1–L4) were obtained with the use of a fan beam in the array mode. Spine scans were analyzed with low-density software.¹⁶ Pediatric whole-body data obtained by means of this method may be confounded by variability in relative skull size¹⁷; therefore, values for whole-body mineral content excluded the skull. Quality-control scans were obtained daily with the use of a spine phantom; the in vitro coefficient of variation was less than 0.6 percent. The in vivo coefficient of variation in adults was less than 1 percent.

STATISTICAL ANALYSIS

Two-sided tests of hypotheses were used, and a P value of less than 0.05 was considered to indicate statistical significance. Mean differences between patients with glucocorticoid-sensitive nephrotic syndrome and controls were assessed by means of the t-test. The sex and race distributions were compared with the use of the chi-square test. The correlations between exposure to glucocorticoids and anthropometric measures were assessed with the use of Pearson product-moment estimates.

The primary outcomes were the bone mineral content of the whole body and the lumbar spine. The assessment of bone content in children and adolescents required adjustment for bone size. The log-linear relationship between the bone mineral content of the spine and the projected bone area is well established.^{18,19} Therefore, the bone mineral content of the spine was assessed with the use of a log-transformed model adjusted for bone area. The bone mineral content of the whole body was assessed with the use of a log-transformed model adjusted for height. A prediction model that

used this approach has been verified in children.²⁰ Furthermore, a recent pediatric study demonstrated that a log-transformed model of whole-body bone mineral content adjusted for height was highly correlated with cortical bone strength ($r=0.63$), as measured by quantitative computed tomography, whereas after adjustment for bone area, these values were not correlated with strength.²¹

The log-transformed models were adjusted for known determinants of bone mineral content that may confound the comparison of patients with glucocorticoid-sensitive nephrotic syndrome and controls. Models were adjusted for Tanner stage (stage 1 served as the reference group) and race (black vs. all others). Tests for interactions between sex and the glucocorticoid-sensitive nephrotic syndrome were not significant; therefore, the results in boys and girls were combined. The assumptions of the regression models were assessed by means of the Shapiro–Wilk test of normality of the residuals and the Cook–Weisburg test for heteroskedasticity.

Obesity in otherwise healthy children is associated with increased bone mineral content of the spine after adjustment for bone area and increased whole-body bone mineral content after adjustment for height.²² Glucocorticoids are associated with obesity; therefore, models were adjusted for the z score for body-mass index, and interaction terms were used to determine whether bone outcomes differed for patients with glucocorticoid-sensitive nephrotic syndrome and control subjects according to the z score for body-mass index.

The effect of glucocorticoid-sensitive nephrotic syndrome in each multivariate model is presented as the adjusted ratio of the outcome measure in the patients divided by the outcome measure in the controls, with 95 percent confidence intervals. The adjusted ratio and confidence intervals were calculated as the exponentiated estimates of the regression variables.

RESULTS

CHARACTERISTICS OF THE SUBJECTS

Sixty patients with glucocorticoid-sensitive nephrotic syndrome and 195 control subjects were enrolled (Table 1). The predominance of boys among the patients reflected the known sex-based pattern of the disease. As compared with the controls, the patients had significantly lower z scores for height ($P=0.008$) and significantly higher z scores for weight ($P=0.003$) and body-mass index ($P<0.001$).

The prevalence of obesity in the control group was consistent with the 16 percent prevalence of obesity in children and adolescents nationwide.²³ In contrast, 38 percent of the patients were obese.

CHARACTERISTICS OF THE NEPHROTIC SYNDROME

The age at onset of the nephrotic syndrome and the extent of glucocorticoid exposure are summarized in Table 2. Forty-seven patients (78 percent) were taking glucocorticoids at the time of the study visit. None had a history of a low-impact fracture,²⁴ and none were taking calcium or vitamin D supplements.

EFFECT OF GLUCOCORTICOID EXPOSURE ON GROWTH AND NUTRITIONAL STATUS

The relationships between each of the measures of exposure to glucocorticoids in Table 2 and the z scores for height and body-mass index were examined. The z score for height was significantly and inversely correlated with the lifetime cumulative dose of glucocorticoids in milligrams ($r = -0.28$, $P = 0.03$) and milligrams per kilogram ($r = -0.38$, $P = 0.003$). The z score for body-mass index was not correlated with any measures of exposure to glucocorticoids.

BONE MINERAL CONTENT

Lumbar Spine

The initial model evaluated the bone mineral content of the spine after adjustment for age and sex. No significant differences were detected between patients and controls. The adjusted ratio for the bone mineral content of the spine in the patients as compared with that in the controls was 0.99 (95 percent confidence interval, 0.92 to 1.05; $P = 0.67$). Subsequently, potential confounders were added to the model, including bone area, Tanner stage, and race (Table 3). Each of these covariates was positively associated with bone mineral content, as anticipated, but the main effect of the nephrotic syndrome was unchanged. The adjusted ratio of the bone mineral content of the spine in the patients as compared with that of the controls was 0.99 (95 percent confidence interval, 0.96 to 1.02; $P = 0.51$). Figure 1 illustrates the bone mineral content of the spine relative to the area of the spine.

The effect of obesity on the bone mineral content of the spine was assessed by adding the z score for body-mass index to the multivariate model. Each one-unit increase in the z score for body-mass

Table 1. Characteristics of Patients with the Glucocorticoid-Sensitive Nephrotic Syndrome and Control Subjects.*

Characteristic	Patients (N=60)	Controls (N=195)	P Value
Age (yr)	9.0±3.4	10.1±4.3	0.09
Sex (no. of subjects)			<0.001
Male	43	80	
Female	17	115	
Black race (%)†	26	39	0.07
Tanner stage (no. of subjects)			0.15
1	47	114	
2	4	27	
3	2	15	
4	4	22	
5	3	17	
Height z score	-0.10±1.00	0.35±1.07	0.008
Weight z score	0.90±1.29	0.44±1.12	0.003
Body-mass-index z score	1.24±1.00	0.34±1.13	<0.001
Obese (%)	38	16	<0.001

* Plus-minus values are means ±SD.

† Race was assigned by the parent or guardian.

Table 2. Disease and Treatment Characteristics of Glucocorticoid-Sensitive Nephrotic Syndrome.*

Characteristic	Mean ±SD	Median	Range
Age at diagnosis (yr)	4.2±3.0	2.9	1.1–12.1
No. of relapses	8.8±9.2	6	1–50
Months of glucocorticoid exposure	53.5±43.6	42.6	2.3–208.2
Cumulative dose of glucocorticoids†			
mg	23,004±20,254	15,223	1524–87,556
mg/kg	907±762	724	24.9–2811
Average dose of glucocorticoids (mg/kg/day)	0.65±0.38	0.59	0.01–1.78
Months since last dose of glucocorticoids	0.95±2.3	0	0–10.6

* Values represent the interval from the first to the last dose of glucocorticoids.

† Values represent prednisone equivalents.

index was associated with a 3 percent increase in the bone mineral content of the spine, after adjustment for the covariates listed in Table 3 (ratio, 1.03; 95 percent confidence interval, 1.02 to 1.04; $P < 0.001$). The bone mineral content of the spine in the patients, after adjustment for bone area, age, sex, Tanner stage, race, and the z score for body-mass index, was significantly lower than that of

Table 3. Multiple Linear Regression Analysis of Bone Mineral Content.

Variable	Ratio*	95% Confidence Interval	P Value
Bone mineral content of spine†			
Bone area	4.14	3.67–4.66	<0.001
Age	1.01	1.00–1.02	0.02
Female sex	1.07	1.04–1.10	<0.001
Tanner stage 2	0.97	0.93–1.02	0.21
Tanner stage 3	1.08	1.01–1.15	0.02
Tanner stage 4	1.15	1.07–1.23	<0.001
Tanner stage 5	1.23	1.13–1.33	<0.001
Black race	1.03	1.00–1.06	0.07
Nephrotic syndrome	0.99	0.96–1.02	0.51
Whole-body bone mineral content‡			
Height	58.5	40.0–84.7	<0.001
Age	1.01	1.00–1.03	0.13
Female sex	1.06	1.01–1.11	0.02
Tanner stage 2	1.00	0.92–1.08	0.95
Tanner stage 3	1.07	0.95–1.19	0.26
Tanner stage 4	1.07	0.96–1.20	0.20
Tanner stage 5	1.17	1.01–1.35	0.03
Black race	1.10	1.05–1.15	<0.001
Nephrotic syndrome	1.11	1.05–1.18	<0.001

* The ratio for each covariate represents the exponentiated regression coefficient. The ratios for age reflect the effect of each one-year increment in age on bone mineral content. The ratios for female sex reflect the value in female subjects as compared with that in male subjects. The ratios for each Tanner stage represent the comparison with Tanner stage 1. The ratios for black race reflect the value in black subjects as compared with all other subjects. For the nephrotic syndrome, the ratios reflect the value in the patients as compared with the value in the controls. The values for the lumbar-spine bone area and height were log-transformed. Therefore, the lumbar-spine bone mineral content increases as a function of bone area to the power of 1.42 [$\log(4.14)=1.42$], and the whole-body bone mineral content increased as a function of height to the power of 4.07 [$\log(58.5)=4.07$].

† $R^2=0.96$.

‡ $R^2=0.94$.

controls (ratio, 0.96; 95 percent confidence interval, 0.92 to 0.99; $P=0.01$). The test for an interaction between the nephrotic syndrome and the z score for body-mass index was not significant ($P=0.69$).

Whole Body

The initial model compared whole-body bone mineral content in patients with that in controls, after adjustment for age and sex, and found no significant differences (ratio, 1.01; 95 percent confidence interval, 0.93 to 1.11; $P=0.73$). The model was

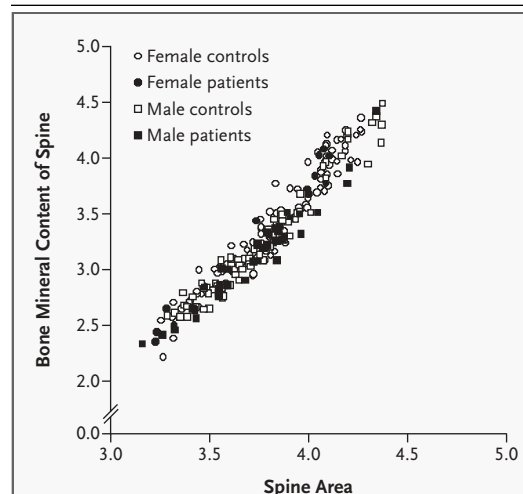


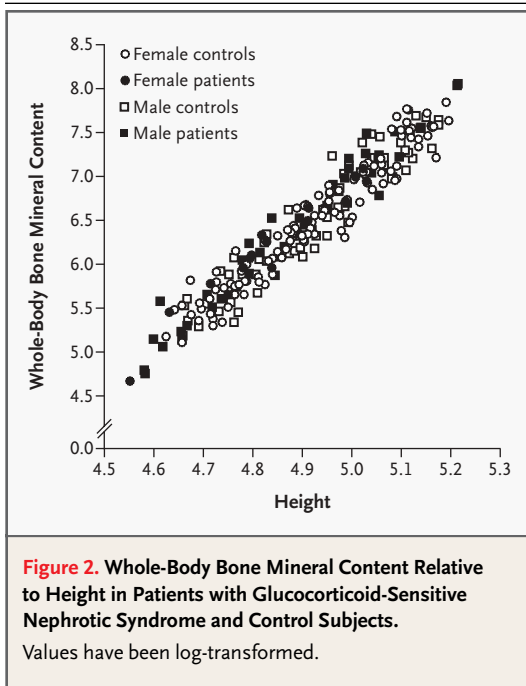
Figure 1. Bone Mineral Content of the Lumbar Spine Relative to Bone Area in Patients with Glucocorticoid-Sensitive Nephrotic Syndrome and Control Subjects. Values have been log-transformed.

then adjusted for height, Tanner stage, and race (Table 3). Whole-body bone mineral content was significantly greater in the patients than in the controls (ratio, 1.11; 95 percent confidence interval, 1.05 to 1.18; $P<0.001$). Figure 2 illustrates the increased whole-body bone mineral content relative to height in patients, as compared with controls.

The z score for body-mass index was added to the multivariate model. Each one-unit increase in the z score was associated with a 14 percent increase in whole-body bone mineral content, after adjustment for the covariates listed in Table 3 (ratio, 1.14; 95 percent confidence interval, 1.12 to 1.15; $P<0.001$). The addition of the z score for body-mass index to the multivariate regression model eliminated the increased whole-body bone mineral content in the patients (ratio, 0.99; 95 percent confidence interval, 0.94 to 1.03; $P=0.55$). The test for an interaction between the nephrotic syndrome and the z score for body-mass index was not significant ($P=0.32$).

DISCUSSION

This study of 60 children and adolescents with glucocorticoid-sensitive nephrotic syndrome who were treated with an average of 23,000 mg of glucocorticoids did not demonstrate the expected deficits in the bone mineral content of the spine or



whole body, as compared with values in a concurrent group of control subjects. Despite reports that glucocorticoids suppress bone formation, whole-body bone mineral content for height was significantly increased in the patients with the nephrotic syndrome, as compared with the controls. This finding was attributed to the markedly increased body-mass index of many of the patients. The bone mineral content of the spine, after adjustment for bone area, age, Tanner stage, sex, and race, was similar in the two groups but was actually lower among the patients, given their increased body-mass index. Glucocorticoid-induced increases in body-mass index may serve to preserve the bone mineral content of the spine and increase whole-body bone mineral content. These analyses demonstrate the importance of the use of an appropriate comparison group of healthy subjects in order to adjust for differences in bone and body size.

Our patients had markedly increased z scores for body-mass index and decreased z scores for height, findings consistent with the expected effects of glucocorticoids. Although the retrospective collection of data on lifetime exposure to glucocorticoids may result in the misclassification of exposure status, the significant correlation between height deficits and the extent of exposure to glucocorticoids provides support for the validity of

these estimates. The z scores for body-mass index fluctuate more widely and rapidly than do those for height, thus probably accounting for the lack of correlation between summary measures of glucocorticoid exposure and the z score for body-mass index at the study visit.

The growing, modeling skeleton is assumed to be more vulnerable than the mature skeleton to the osteoblast-inhibiting effects of long-term exposure to glucocorticoids, with consequent long-term deficits in cortical and trabecular bone mass. A case series of bone biopsies that included six children with glucocorticoid-dependent nephrotic syndrome demonstrated an inverse correlation between the rate of bone formation and the dose of prednisone at the time of biopsy; however, the trabecular structure was not typical of that resulting from glucocorticoid use.²⁵ A recent study in rabbits demonstrated that dexamethasone-induced osteoporosis in trabecular and cortical bone during growth was reversed through endochondral bone formation once dexamethasone was discontinued.²⁶ In patients with glucocorticoid-sensitive nephrotic syndrome, glucocorticoids are tapered by giving them on alternate days between relapses and may be discontinued intermittently. The preserved bone mineral content of the spine and increased whole-body bone mineral content in our patients may reflect the unique ability of the growing skeleton to sustain transient glucocorticoid-induced reductions in bone formation and to recover during remission intervals.

Possible mechanisms for the independent positive association between bone mineral content and z scores for body-mass index include hormonal influences, such as increased conversion of androstenedione to estrogen or increased circulating leptin levels. In addition, increased biomechanical loading as a result of increased body weight may also contribute to the increased bone mineral content. The predominantly cortical whole-body bone mineral content in our patients was significantly higher than that in controls, a difference attributable to the increased body-mass index of our patients. However, the predominantly trabecular bone mineral content of the spine was decreased after adjustment for the body-mass index. This finding is consistent with reports that cortical bone mineral content increases with mechanical loading in children²⁷ and with reports in adults that trabecular bone is more susceptible than cortical bone to the effects of glucocorticoids.

Gulati et al. recently conducted a study in India using dual-energy x-ray absorptiometry to determine the areal bone mineral density of the spine in 100 children with the nephrotic syndrome, concluding that the majority had osteopenia.²⁸ The patients' age, duration of disease, and cumulative exposure to glucocorticoids were similar to those of our patients. Sixty-one percent of their subjects were given a diagnosis of osteopenia (areal bone mineral density z score, less than -1), and 22 percent received a diagnosis of osteoporosis (z score, less than -2.5). The deficits in areal bone mineral density and cumulative exposure to glucocorticoids were greater in the children with glucocorticoid-dependent nephrotic syndrome, frequent relapses, or glucocorticoid-resistant nephrotic syndrome than in those with infrequent relapses.

Two important limitations may explain the findings of Gulati et al.²⁸ First, the use of dual-energy x-ray absorptiometry to determine bone mineral density is flawed in children owing to the confounding effect of bone size.^{18,29,30} Dual-energy x-ray absorptiometry provides a two-dimensional estimate of bone mineral content divided by bone area (expressed as grams per square centimeter). This areal bone mineral density is not a measure of density (expressed as grams per cubic centimeter), because it provides no information about bone depth. Areal bone mineral density inherently underestimates the bone density of shorter persons. Gulati et al. provided no information regarding z scores for height; however, it is likely that the lower z scores for areal bone mineral density in the patients with glucocorticoid-dependent nephrotic syndrome and frequent relapses were due to lower z scores for height. Second, in the absence of data from concurrent controls or normative data on Indian children, the investigators used the Hologic pediatric reference database, which is not specific for sex, to generate z scores. A comparison of pediatric data obtained by dual-energy x-ray absorptiometry demonstrated that, as compared with sex-specific databases, the Hologic database resulted in four times as many boys' being classified as having osteoporosis.³¹ Eighty-three percent of the subjects in the study by Gulati et al. were male.

Differences in the study populations also most likely contributed to their findings. Gulati et al. included subjects with glucocorticoid-resistant nephrotic syndrome, which may result in bone and mineral abnormalities independent of the effects

of glucocorticoids. In addition, the mean body-mass index in these subjects (16.5) was markedly lower than in our patients (21.4). Differences in nutritional status between Indian and American children may contribute to differences in bone health.

Numerous studies have reported decreased areal bone mineral density on dual-energy x-ray absorptiometry in association with glucocorticoid therapy in children and adolescents with chronic inflammatory conditions, such as Crohn's disease,³² organ transplantation,³³ juvenile rheumatoid arthritis,³⁴ juvenile dermatomyositis,³⁵ and cystic fibrosis.³⁶ Although decreased height may contribute to these observations, these children are at risk for bone loss caused by increased levels of inflammatory cytokines, malnutrition, and decreased weight-bearing activity. Recent advances in the understanding of osteoclast biology have focused attention on the pathophysiology of bone loss in inflammatory conditions and the critical role of cytokines in promoting bone resorption.³⁷ Inflammation promotes bone resorption, and glucocorticoids suppress bone formation. This uncoupling of the components of bone turnover may have severe consequences in the growing skeleton. Therefore, the preservation of bone mass in patients with glucocorticoid-sensitive nephrotic syndrome may be due to the absence of a persistent underlying inflammatory condition and may be less germane to other conditions.

The clinical significance of glucocorticoid-induced osteoporosis in children may be immediate, resulting in low-impact fractures, or delayed, owing to suboptimal accrual of peak bone mass. None of our patients had sustained a low-impact fracture. Furthermore, our finding of an increased whole-body bone mineral content in relation to height provided reassurance that peak bone mass will be normal in these patients. Nonetheless, glucocorticoids may have important sustained effects on the microarchitecture or mineralization of bone that require future study. In addition, case-control studies of the effect of obesity on the risk of fracture in children have yielded conflicting results.^{38,39}

Our findings illustrate the importance of the use of appropriate reference data and consideration of growth and body composition in the assessment of bone health in children. The failure to consider these issues may result in the inappropriate treatment of children with bone-active therapies or inappropriate enrollment in treatment trials.

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