Glucocorticoid-Induced Osteoporosis in Children: Impact of the Underlying Disease

Mary B. Leonard, MD, MSCE
Department of Pediatrics, Children’s Hospital of Philadelphia, Philadelphia, Pennsylvania; Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

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ABSTRACT

Glucocorticoids inhibit osteoblasts through multiple mechanisms, which results in significant reductions in bone formation. The growing skeleton may be especially vulnerable to adverse glucocorticoid effects on bone formation, which could possibly compromise trabecular and cortical bone accretion. Although decreased bone mineral density has been described in various pediatric disorders that require glucocorticoids, and a population-based study reported increased fracture risk in children who require >4 courses of glucocorticoids, some of the detrimental bone effects attributed to glucocorticoids may be caused by the underlying inflammatory disease. For example, inflammatory cytokines that are elevated in chronic disease, such as tumor necrosis factor α, suppress bone formation and promote bone resorption through mechanisms similar to glucocorticoid-induced osteoporosis. Summarized in this review are changes in bone density and dimensions during growth, the effects of glucocorticoids and cytokines on bone cells, the potential confounding effects of the underlying inflammatory-disease process, and the challenges in interpreting dual-energy x-ray absorptiometry results in children with altered growth and development in the setting of glucocorticoid therapy. Two recent studies of children treated with chronic glucocorticoids highlight the differences in the effect of underlying disease, as well as the importance of associated alterations in growth and development.
URING CHILDHOOD AND adolescence, skeletal development is characterized by gender-, maturation-, and race-specific increases in cortical dimensions and trabecular density. The 2000 National Institutes of Health Osteoporosis Prevention, Diagnosis, and Therapy Consensus Development Conference identified bone accrual during childhood as a critical determinant of lifelong skeletal health. The authors of the resulting consensus statement1 specifically called for research to determine the impact of chronic diseases and glucocorticoid therapy on bone accrual in children.

Glucocorticoid-induced osteoporosis (GIO) is the most common cause of secondary osteoporosis in adults and is the result of profound effects of glucocorticoids on bone cells.2 Glucocorticoids inhibit osteoblastogenesis and promote osteoblast apoptosis, which results in significant reductions in bone formation.3 Studies in adults have demonstrated that glucocorticoids cause rapid, dose-dependent bone loss and increased fracture risk.4 The growing skeleton may be especially vulnerable to adverse glucocorticoid effects on bone formation, which could possibly compromise trabecular and cortical bone accretion.

Glucocorticoids are used in myriad pediatric diseases. Decreased bone mineral density (BMD) has been described in various pediatric disorders that require glucocorticoids, including asthma, juvenile rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, and organ transplantation.5–8 A population-based study reported increased fracture risk in children who required >4 courses of glucocorticoids.9 Although these studies demonstrate a correlation between glucocorticoids, bone deficits, and fracture risk, some of the detrimental bone effects attributed to glucocorticoids may be caused by the underlying inflammatory disease. For example, inflammatory cytokines, such as tumor necrosis factor α (TNF-α), suppress bone formation, promote bone resorption, and are increased in rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus.10 Furthermore, alterations in growth related to glucocorticoids and the underlying disease may confound dual-energy x-ray absorptiometry (DXA) measures of BMD.

Summarized in this review are changes in bone density and dimensions during growth, the effects of glucocorticoids and cytokines on bone cells, the potential confounding effects of the underlying inflammatory-disease process, and the challenges in interpreting DXA results in children with altered growth and development in the setting of glucocorticoid therapy. Two recent studies of children who were treated chronically with glucocorticoids highlight the differences in the effect of underlying disease, as well as the importance of concurrent alterations in body composition.

**BONE MODELING AND REMODELING**

The shape and structure of bones are continuously modified and renovated by the 2 processes of modeling and remodeling, both of which result in the replacement of old bone with new bone. Remodeling is the major process in adults and does not result in a change of the bone shape. Remodeling takes place in the basic bone multicellular units on the trabecular surface and within the cortical bone. Normally, bone resorption by osteoclasts is followed by bone formation by osteoblasts; teams of osteoclasts and osteoblasts are juxtaposed in the bone multicellular units, and bone resorption and formation are coupled. In the young-adult skeleton, the newly formed bone completely replaces the bone lost in the resorption phase. This process is vital for repairing microdamage and maintaining skeletal integrity. After midadulthood, the amount of resorption slightly exceeds formation, which results in a negative bone balance with aging.

In contrast, modeling results in new bone formed at a location different from the site of bone resorption. This process results in an increase in bone diameter and modification of bone shape. Figure 1 summarizes the complex interplay of site-specific bone-resorption and -formation activities that are necessary to achieve bone growth from length A to B.11 Growth in the diameter of the cortical shaft is the result of bone formation at the...
outer (periosteal) surface and bone resorption at the inner (endosteal) surface. Simultaneously, the growth plate moves upward and the wider parts of the bone must be reshaped into a diaphysis. This reshaping is accomplished by continuous resorption by osteoclasts beneath the periosteum. The impact of glucocorticoid therapy on bone modeling and structure has not been well characterized.

Trabecular BMD, as measured by quantitative computed tomography (QCT), does not increase before puberty.12,13 During puberty, trabecular BMD increases significantly as a result of increases in trabecular thickness.14 The pubertal increases in BMD are comparable in girls and boys but are significantly greater in black compared with white adolescents.12,13,15 Studies of cortical BMD and dimensions in the appendicular skeleton produced conflicting results, potentially because of differences between the upper and lower extremities and in measurement techniques. Most studies have reported significant increases in cortical BMD with age (reviewed by Hogler et al16). An early study of cortical dimensions, based on two-dimensional radiogrammetry, concluded that the greater cortical bone mass in male subjects was attributable to gender differences in the rate of endosteal apposition and resorption.17 Subsequent peripheral QCT studies in the upper extremities also suggested gender differences in the endocortical surface, with constant dimensions with age in female subjects and increasing dimensions with age in male subjects.18 Furthermore, later age at menarche in girls is associated with greater endosteal dimensions in adulthood.19 In contrast, studies in the weight-bearing femur15,16 and tibia20 failed to demonstrate gender differences in endocortical resorption. Given the distinct effects of puberty and gender on trabecular and cortical bone, the structural implications of glucocorticoid therapy may differ in pubertal and prepubertal children.

**FUNCTIONAL MUSCLE-BONE UNIT**

According to Wolff’s law, bone grows in response to the magnitude and direction of the forces to which it is subjected.21 This response keeps mechanically induced deformation of bone (strain) at a set point. Bone deformation induces canalicular fluid flow that is detected by osteocytes.22 Osteocytes transduce signals that induce an anabolic response to increase bone strength.23 This capacity of bone to respond to mechanical loading with increased bone strength is greatest during growth24; mechanical signals that are osteogenic in the young skeleton fail to stimulate bone formation in the mature skeleton.25 Hormones and nutrients influence mechanical loads by influencing linear growth and muscle mass and may alter the muscle-bone set point.26

The observed strong correlation between muscle mass and bone mass has prompted numerous investigators to advocate a multistage algorithm for the assessment of bone measures relative to muscle mass in children. Proposed strategies include assessing bone mineral content (BMC) relative to body weight or lean mass and varied multistage models for BMC that incorporate age, ethnicity, height, weight, bone area, and pubertal stage.27–32

Glucocorticoids are also well known to cause muscle wasting.33 Muscle weakness results from muscle atrophy because of accelerated catabolism of muscle proteins. Therefore, glucocorticoid-induced myopathy may contribute to bone deficits via the functional muscle-bone unit.

**GLUCOCORTICOID EFFECTS ON BONE FORMATION AND RESORPTION**

Decreased bone formation is the primary mechanism for bone loss in GIO.2 Mesenchymal stem cells, which also give rise to adipocytes, myoblasts, and chondrocytes, differentiate into osteoblasts. Glucocorticoids shift the cellular differentiation away from osteoblasts and toward adipocytes and prevent the termination differentiation of osteoblasts.34 Osteoblast numbers are decreased further by glucocorticoid-induced increases in osteoblast apoptosis.3 In addition, glucocorticoids inhibit osteoblast production of bone-matrix components.35 Finally, glucocorticoids suppress the synthesis of insulin-like growth factor I, an agent that enhances bone formation.36 The cellular response to glucocorticoids also includes an early phase of increased bone resorption, which is probably a result of the increased expression of receptor activator of nuclear factor κB ligand (RANKL) and decreased expression of osteoprotegerin; increased RANKL and decreased osteoprotegerin both promote osteoclastogenesis, as detailed below.37,38 However, typically, a more chronic state of decreased bone resorption develops as a result of loss of cell signaling to osteoclast progenitors.39 Decreased bone formation and resorption have also been observed in the setting of increased endogenous glucocorticoid production (eg, in burn injury in children40). The effects of glucocorticoids on bone cells are summarized in Table 1.

Patients treated with glucocorticoids have an underlying disease that frequently also carries a risk of osteoporosis. Therefore, the independent effects of glucocorticoids on bone turnover and bone structure during growth are not readily apparent from clinical studies. However, recent animal models demonstrated that glu-

<table>
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<th>TABLE 1</th>
<th>Glucocorticoid Effects on Bone Cells</th>
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<tr>
<td>Decrease in bone formation</td>
<td>Shift in cellular differentiation of stem cells away from osteoblasts</td>
</tr>
<tr>
<td>Inhibition of osteoblast production of bone matrix</td>
<td>Induction of apoptosis of osteoblasts</td>
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<tr>
<td>Decrease in synthesis of insulin-like growth factor I</td>
<td>Transient increase in bone resorption</td>
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<tr>
<td>Promotion of osteoclastogenesis by increasing RANKL and decreasing osteoprotegerin expression in stromal and osteoblastic cells</td>
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corticoid administration during growth result in decreased bone formation, decreased bone resorption, reductions in the age-dependent increases in trabecular bone mineral and trabecular thickness, and reductions in linear growth and accrual of cortical thickness in the femur.\(^41,42\) These deficits were associated with decreased bone strength in the vertebrae and femur in mechanical testing.\(^41,42\) It is notable that it is unclear if the reductions in femoral cortical thickness were proportionate to the significant reductions in bone length; that is, did the bones have normal cortical thickness and strength relative to the shorter length?

**OSTEOMMUNOLOGY: THE INTERPLAY BETWEEN THE IMMUNE SYSTEM AND BONE**

Three groups of cytokines are particularly important in bone physiology: interleukin 6 (IL-6), TNF-\(\alpha\), and IL-1.\(^38\) The effects of TNF-\(\alpha\) on bone formation are strikingly similar to the effects of glucocorticoids. TNF-\(\alpha\) inhibits osteoblast differentiation, inhibits osteoblast synthesis of collagen, and promotes osteoblast apoptosis.\(^43\) The effects of selected inflammatory cytokines on bone cells are summarized in Table 2.

RANKL stimulates osteoclast differentiation and activation and inhibits osteoclast apoptosis. In contrast, osteoprotegerin acts as a decoy receptor for RANKL and acts as an inhibitor of bone resorption. TNF-\(\alpha\), IL-1, and IL-6 exert their osteoclastogenic effects through increased RANKL, as well as through other autocrine and paracrine pathways that are independent of RANKL.\(^44–46\)

It is notable that some studies of bone resorption markers in inflammatory conditions have shown increased resorption,\(^45\) whereas another study demonstrated decreased resorption in the setting of increased endogenous cortisol.\(^46\) It has been hypothesized that the number of osteoblasts are decreased to the point that RANKL production is reduced.

In addition to detrimental effects on bone metabolism, inflammatory cytokines such as TNF-\(\alpha\) and IL-1 also adversely affect whole-body protein and energy metabolism, which is similar to glucocorticoid effects.\(^48\) Specifically, TNF-\(\alpha\)-induced activation of nuclear factor \(\kappa B\) inhibits skeletal-muscle differentiation by suppressing MyoD messenger RNA.\(^49\) Therefore, cytokine-induced reductions in muscle mass may contribute to bone deficits in chronic inflammatory conditions through the functional bone-muscle unit described above.

**TABLE 2 Inflammatory Cytokine Effects on Bone Cells**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cytokine(s)</th>
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<tbody>
<tr>
<td>Decrease in bone formation</td>
<td>TNF-(\alpha) inhibits osteoblast differentiation</td>
</tr>
<tr>
<td></td>
<td>TNF-(\alpha) inhibits collagen synthesis in osteoblasts</td>
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<tr>
<td></td>
<td>TNF-(\alpha) promotes osteoblast apoptosis</td>
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<tr>
<td>Increase in bone resorption</td>
<td>IL-1, TNF-(\alpha), and IL-6 increase RANKL and promote osteoclastogenesis</td>
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Infliximab, a chimeric monoclonal antibody to TNF-\(\alpha\), is effective in both inducing and maintaining clinical remission in patients with refractory Crohn disease and in patients with inflammatory arthropathies. Recent observational studies of adults who were treated with infliximab highlight the importance of TNF-\(\alpha\) in the bone and muscle deficits observed in these diseases; infliximab therapy was associated with significant increases in markers of bone formation, decreases in markers of bone resorption, increases in BMD, and increases in lean mass (without changes in fat mass).\(^47,50–52\)

**LIMITATIONS OF DXA IN THE ASSESSMENT OF GIO IN CHILDREN**

DXA is, by far, the most widely used technique for measuring bone mass in children. However, DXA is a two-dimensional technique in which bone is presented as the combined sum of cortical and trabecular bone within the projected bone area, concealing the distinct structural characteristics. DXA provides an estimate of BMC per anatomic region; dividing the BMC (in grams) by the projected area of the bone (in centimeters squared) then derives areal BMD (in grams per centimeters squared). This BMD is not a measure of volumetric density (in grams per centimeters cubed) because it provides no information about bone depth. Bones of larger width and height are thicker. Because bone thickness is not factored into DXA results, reliance on areal BMD systematically underestimates bone density in shorter people. In evaluating children who receive glucocorticoid therapy, one could falsely attribute the decreased areal BMD for age as evidence for osteopenia rather than a glucocorticoid-induced reduction in height for age.

Two recent studies illustrated that failure to consider the confounding effect of height results in an overestimation of bone deficits in children with chronic disease. First, Wren et al\(^53\) compared DXA areal BMD and QCT volumetric BMD \(z\) scores in the spine of 200 healthy children and 200 chronically ill children. The hypothesis of the study was that DXA results in the overdiagnosis of osteoporosis (defined as a \(z\) score of less than \(-2.0\)) in children with poor growth. Consistent with this hypothesis, a significantly greater proportion of children were classified as osteopenic according to DXA (76 of 400) compared with QCT (25 of 400), particularly among children below the 5th percentile for height and/or weight for age. Using QCT as the standard for this comparison, the specificity of a DXA \(z\) score less than \(-2.0\) was 94% among healthy children but only 74% among the chronically ill children; that is, among the 179 ill children with QCT \(z\) scores greater than \(-2.0\), 47 (26%) had DXA \(z\) scores less than \(-2.0\). Second, Gafni and Baron\(^54\) reported that inattention to the confounding effect of short stature resulted in inappropriate referral for possible inclusion in a childhood osteoporosis protocol on the basis of low DXA-derived spine areal BMD.
TWO MODELS OF GIO IN CHILDREN: CROHN DISEASE AND NEPHROTIC SYNDROME

The following summary considers 2 studies recently reported by our group of children who were receiving glucocorticoids chronically for Crohn disease or steroid-sensitive nephrotic syndrome (SSNS). Crohn disease was associated with significant reductions in BMI and whole-body BMC.32 In contrast, SSNS was associated with greater BMI, normal spine BMC, and greater whole-body BMC compared with controls.55 Fig 2 illustrates whole-body BMC relative to height in the subjects with Crohn disease (Fig 2A) and SSNS (Fig 2B), each compared with healthy controls. Differences in the characteristics of the underlying disease are considered as an explanation for these different patterns of bone health in children treated with chronic glucocorticoids. Multivariate analyses are presented to address the confounding effects of growth and maturation.

Crohn Disease

Crohn disease is an idiopathic, lifelong, destructive chronic inflammatory condition of the gastrointestinal tract. The pathogenesis has been linked to genetic and environmental factors that lead to sustained activation of the mucosal immune response.56 Disease rates are highest in Westernized countries, and the incidence rate in children is increasing.57–60 The incidence of pediatric Crohn disease is ~7 new cases per 100 000 children per year.60 In addition to the usual symptoms of diarrhea, abdominal pain, weight loss, anemia, and rectal bleeding, children may exhibit growth failure years before disease diagnosis.61,62 Anorexia, malabsorption, and increased metabolic demands all contribute to poor growth. Small bowel disease may impair absorption of iron, zinc, folate, and vitamin B12.61 High-dose glucocorticoids are widely used in the treatment of Crohn disease.56

Osteopenia has been well documented in children and adults with inflammatory bowel disease.63–67 Six children with spine fractures were identified at our institution, and hip, spine, and forearm fractures are significantly increased in adults with Crohn disease.68–73 Cellular inflammatory pathways in Crohn disease activate the protean transcriptional regulatory factor nuclear factor κB with increased production of a variety of cytokines such as IL-6 and TNF-α.56 Serum from children with Crohn disease impairs osteoblast function and differentiation in vitro.74,75

We recently reported significant bone and muscle deficits in a cross-sectional study of children and young adults with established Crohn disease.32,76 Whole-body BMC, lean mass, and fat mass were assessed by DXA in 104 subjects with Crohn disease and 233 healthy controls, 4 to 26 years of age. Individuals with Crohn disease had significantly lower height-for-age, BMI-for-age, and whole-body lean-mass-for-height z scores than healthy controls (all P < .001). Ninety percent of subjects with Crohn disease had been treated with glucocorticoids. The cumulative exposure averaged 7900 mg over 15.2 months, which resulted in an average dose of 0.50 mg/kg per day.

The least-adjusted models assessed whole-body BMC in subjects with Crohn disease compared with controls, adjusted for age and race, and revealed substantial deficits (Table 3). Assessment of BMC without consideration of the decreased skeletal size for age in subjects with Crohn disease may overestimate bone deficits. Accordingly, the second model was also adjusted for height. Adjustment for height attenuated the Crohn disease effect; however, significant BMC deficits persisted in male and female subjects with Crohn disease compared with controls. To determine if delayed pubertal maturation for age contributed to the decreased BMC in those with Crohn disease, the third model included Tanner stage. Adjustment for delayed pubertal maturation did not appreciably change the estimate of BMC deficits in the subjects with Crohn disease. The fourth and final
model, adjusted for lean mass, eliminated significant BMC deficits in the subjects with Crohn disease.

None of the glucocorticoid measures were significantly correlated with BMC-for-height z scores. However, height z score was negatively and significantly associated with duration of glucocorticoid therapy \( (r = -0.24; \ P = .02) \) and cumulative (milligrams per kilogram) glucocorticoid dose \( (r = -0.36; \ P < .001) \). Parenteral nutrition, isolated upper tract disease, hypoalbuminemia, nasogastric feeding, and decreased BMI z scores were associated with decreased BMC-for-height z scores.

A subsequent analysis quantified lean and fat mass in these same subjects with Crohn disease, relative to height and pubertal maturation, compared with healthy controls.\(^{26}\) Although Crohn disease was associated with significant deficits in lean mass, adjusted for height, age, race, and Tanner stage \( (P = .003) \), fat mass was not decreased (mean fat-mass-for-height z score = \(-0.04 \pm 0.86\)). Within the controls, fat mass for height was positively associated with lean mass for height \( (r = 0.41; \ P < .0001) \); this association was absent in those with Crohn disease. Therefore, subjects with Crohn disease exhibited significant deficits in lean mass with preserved fat mass, which is consistent with inflammatory cachexia.

### Steroid-Sensitive Nephrotic Syndrome

In contrast with Crohn Disease, childhood SSNS syndrome provides a clinical model of chronic glucocorticoid therapy in the absence of significant underlying disease activity. The nephrotic state is clinically quiescent as long as high-dose glucocorticoid therapy is continued. Unfortunately, SSNS relapses in the majority of children when the glucocorticoids are reduced, which results in protracted, repeated courses of glucocorticoids. The standard prednisone dose for relapses is 2 mg/kg per day,\(^{77}\) which far exceeds the 5 mg/day that is considered a risk factor for GIO in adults.\(^{5}\) Although SSNS relapses are associated with transient increases in cytokines, these abnormalities promptly resolve with glucocorticoid therapy and disease remission.\(^{78}\) Therefore, we propose SSNS as a clinical model without significant systemic inflammatory involvement to examine the effects of glucocorticoids on the growing skeleton.

We examined spine and whole-body BMC in a cross-sectional study of 60 children and adolescents with established SSNS and 195 healthy controls.\(^{35}\) The subjects with SSNS had received an average of 23 000 mg of glucocorticoids over a 4-year interval, which resulted in an average dose of 0.65 mg/kg per day. Subjects with SSNS had significantly decreased height \( (P = .008) \) and increased BMI z scores \( (P < .001) \) compared with controls. The prevalence of obesity in the control group was 16%, consistent with the 15.5% prevalence of obesity in children and adolescents nationwide.\(^{79}\) In contrast, 38% of the subjects with SSNS were obese. Among the subjects with SSNS, height z score was significantly and negatively correlated with the lifetime cumulative milligrams \( (r = -0.28; \ P = .03) \) and cumulative milligrams per kilogram \( (r = -0.38; \ P = .003) \) of glucocorticoids. BMI z score was not correlated with glucocorticoid measures.

Spine BMC, adjusted for bone area, age, gender, Tanner stage, and race, did not differ significantly between patients and controls \( (P = .51) \). We had documented that obesity, in otherwise healthy children, was associated with a significant increase in whole-body, hip, and spine BMC and bone size.\(^{40,41}\) Therefore, these models were adjusted for BMI z score. In the adjusted model, spine BMC was 4% lower in subjects with SSNS than controls (ratio: 0.96 [95% confidence interval: 0.92 to 0.99]; \( P = .01) \). Whole-body BMC, adjusted for height, age, gender, Tanner stage, and race, was 11% higher in subjects with SSNS than controls (ratio: 1.11 [95% CI: 1.05 to 1.18]; \( P < .001) \); however, the addition of BMI z score to the model eliminated the association with SSNS (ratio: 0.99 [95% CI: 0.94 to 1.03]; \( P = .55) \).

These data suggested that intermittent treatment with high-dose glucocorticoids during growth was not associated with bone deficits relative to age, bone size, gender, and maturation in SSNS. Glucocorticoid-induced obesity was associated with increased whole-body BMC and maintenance of spine BMC. Subsequent analyses were performed to examine the relations between obesity and growth in nephrotic syndrome compared with controls.\(^{85}\) Height z score was positively associated with BMI z score among subjects with nephrotic syndrome and controls. The mean height z score in those with nephrotic syndrome was \(-0.08 \) (95% CI: \(-0.37 \) to 0.21), which was significantly decreased given the degree of obesity. The overall height was normal for age because of a mitigating effect of elevated BMI on glucocorticoid-induced growth retardation.

| TABLE 3 | Hierarchical Models of Whole-Body BMC z Scores in Crohn Disease\(^{32}\) |
| Models | Males | | Females |
| Age and race | \(-1.16 \) (\(-1.51 \) to \(-0.82\)) | <0.001 | \(-0.61 \) (\(-0.95 \) to \(-0.27\)) | 0.01 |
| Height, age, and race | \(-0.63 \) (\(-0.95 \) to \(-0.30\)) | <0.001 | \(-0.44 \) (\(-0.81 \) to \(-0.06\)) | 0.2 |
| Height, age, race, and Tanner stage | \(-0.50 \) (\(-0.85 \) to \(-0.15\)) | <0.001 | \(-0.35 \) (\(-0.72 \) to 0.02) | 0.06 |
| Height, age, race, Tanner stage, and lean mass | \(-0.19 \) (\(-0.43 \) to 0.06) | 0.13 | \(-0.05 \) (\(-0.34 \) to 0.25) | >2 |
These disparate chronic childhood diseases that are treated chronically with high-dose glucocorticoids highlight the important impact of the underlying disease and its effect on growth and nutrition. These analyses also demonstrate the importance of concurrent healthy controls to adjust for differences in growth and body composition across the broad age range of subjects. It is critical to note that the absence of a bone deficit after adjustment for lean mass in the subjects with Crohn disease does not imply that the bones are normal or adequate. Growth, in the absence of normal loading, results in bones that are adapted to their diminished functional requirement, with decreased mass, size, and strength. These bones may be inadequate to withstand even minor trauma.

A study is currently underway in an inception cohort of children at the time of diagnosis of Crohn disease or SSNS. In the study we are examining bone (as measured by QCT), body composition, growth, maturation, and cytokine levels before glucocorticoid therapy and during the first year of therapy. The accurate characterization of glucocorticoid and disease effects on skeletal development is necessary to identify and evaluate targeted therapies to optimize skeletal architecture and peak bone mass.

ACKNOWLEDGMENTS

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