Longitudinal Assessment of Growth, Mineral Metabolism, and Bone Mass in Pediatric Crohn’s Disease

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Summary: In children with inflammatory bowel disease, controversy continues about the use of long-term alternate day prednisone therapy (ADP) to suppress disease activity and to encourage appetite and growth. One possible side effect of both disease process and prednisone therapy is risk of development of osteoporosis. To evaluate this risk factor, growth, biochemical indices of mineral and vitamin D status, and bone mass were measured in nine adolescents with Crohn’s disease (CD) who were treated with ADP (0.3 mg/kg >3 months per year) compared with eight adolescents treated with minimal ADP exposure (<3 months per year). Single photon densitometry was used to measure bone mineral mass at the 1/3 distal radius three times over 2 years. Mean age of the 17 CD boys was 13.9 ± 2.1 years at baseline. CD patients had lower bone BMC/BW mineral content/bone width (BMC/BW) compared with age- and height-matched normal boys at all times. The difference was less when compared to height-matched normal values as CD patients were shorter than healthy reference boys. Plasma 1,25-dihydroxyvitamin D, alkaline phosphatase, and parathyroid hormone significantly increased with treatment of disease but there were no differences between treatment groups. CD patients treated with ADP had similar heights and weights at baseline and demonstrated similar linear growth over 2 years (9.1 cm/2 years) to CD patients without ADP (10.3 cm/2 years). In both groups, BMC/BW increased significantly from year 1 to year 2, but absolute values for bone mass did not differ between the groups. These data suggest that over a 2-year treatment period male CD patients with chronic low-dose ADP exposure achieve linear growth rates and maintain bone mineralization at least as well as male CD patients who do not receive ADP. Key Words: Growth—Mineral metabolism—Bone mass—Crohn’s disease.

Children with Crohn’s disease (CD) risk impaired bone mineralization from both the effects of the disease and the methods of treatment. Bone mineralization reflects growth and sexual development which may be delayed in 30% of pediatric patients with CD (1,2). Growth delay in CD is not fully understood but is influenced by decreased nutrient intake, intestinal malabsorption, and increased intestinal losses associated with protein-losing enteropathy (1,3,4). Corticosteroids used to suppress inflammation in CD may impair mineral homeostasis through a variety of mechanisms in the intestine, bone, kidney, and parathyroid gland (5). Calcium malabsorption (6) and rapid decreases in total body calcium (7) have been documented in patients with inflammatory diseases. The degree to which the calcium deficit is related to the direct effects of corticosteroids or disease related malabsorption is not well delineated (8).

Previous studies have shown osteoporosis and osteomalacia confirmed by bone biopsy in adult patients with CD (9,10). Prolonged daily exposure to corticosteroids clearly results in delayed growth and sexual maturation in children and puts them at high risk for decreased bone mineralization. However, low-dose alternate-day corticosteroids may be used to stimulate appetite and maintain growth in pediatric patients (11). Clinicians differ as to the relative risk of growth impairment and bone demineralization versus the possibility of improved well-
being, nutrition, and growth associated with disease suppression on low-dose alternate-day corticosteroid therapy. Accordingly, we have examined the influence of alternate-day corticosteroid treatment on growth, bone mineralization, and mineral biochemical status in our pediatric CD patients.

METHODS

Patients

Consecutively referred patients to the Regional Pediatric Gastroenterology Clinic, Children's Hospital at Chedoke-McMaster were followed for 2 years after initial study. Most patients were studied within 1 month of diagnosis. Four patients were enrolled 1–3 years after diagnosis on referral for persistent growth failure. Crohn's disease was diagnosed by clinical history, characteristic clinical and radiologic/colonoscopic findings with histologic examination of biopsy material when available. Informed consent was obtained for collection of serum and urine samples and bone densitometry. Patients were treated according to clinical judgment. Sulfasalazine (50 mg/kg), if tolerated, was used for initial management. Corticosteroids were begun in the absence of a clinical response within 2 weeks. When used, corticosteroids were administered as prednisone, 2 mg (maximum 50 mg/kg/day) consolidated into a single morning dose after 1 week. Prednisone was weaned over 8–12 weeks to a low-dose (0.3 mg/kg) alternate-day regimen and continued if required to maintain normal activities of daily living, adequate nutrient intake, and optimal growth. In a second group, prednisone could be weaned and discontinued within 8–12 weeks of initiation. Exacerbations were treated as outlined above. This resulted in two groups, one in which prednisone was used briefly to achieve initial remission and discontinued and a second group that was maintained on chronic low-dose alternate-day prednisone for the period of the study. Thus the bias in the study, if any, was to treat more severely affected patients with alternate-day prednisone therapy.

Regular nutritional counseling for all patients emphasized adequate energy intake and the avoidance of high-residue foods (nuts and corn products) in patients with strictures of the terminal ileum. For data analysis patients were divided into two groups: long-term low-dose alternate-day prednisone (ADP), i.e., those exposed to prednisone for >12 weeks per year, and those with <12 weeks/year of prednisone treatment (non-ADP). We confine this report to male CD patients because of sex-related differences in bone mineralization during growth and sexual maturation.

Data Collection

At baseline and at two subsequent annual visits, clinical, biochemical, urine, and bone density measurements were performed. Patients were assessed by a nurse research coordinator and a single physician (R.M.I.). Clinical examination included assignment of sexual maturity according to Tanner (12). A standardized clinical score for disease activity [Crohn's disease activity index (CDAI) range, 0–450] (13) was assigned for disease activity based on patient diaries of the previous week. This measure includes specific symptomatic criteria as well as selected laboratory measures. Single observer stadiometric height in sock feet and balance beam weight were obtained. Acid-washed bottles were used for 24-hour urine collection for calcium, phosphorus, magnesium, and creatinine. A blood sample was obtained for complete blood count and erythrocyte sedimentation rate, serum protein, albumin, ionized and total calcium, phosphorus, alkaline phosphatase, magnesium, parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OHD), 1,25-dihydroxyvitamin D (1,25(OH)₂D), and osteocalcin. Yearly weight and height velocity were calculated and compared with Tanner and Whitehouse growth charts (14).

Biochemical Methods

Blood and urine levels of calcium, magnesium, phosphorus, and alkaline phosphatase were measured by standard methods in clinical biochemistry; pH, and ionized calcium by ion-selective electrodes (ICal, Radiometer, Copenhagen, Denmark); creatinine by the double-slide method with the Ektakem 700 instrument (Eastman Kodak Co., Rochester, NY, U.S.A.). PTH was quantitated with a radioimmunne C-terminal assay test kit (No. 1300, Immuno Nuclear Corp., Stillwater, MN, U.S.A.) that has a stated upper limit of normal of 0.88 pM. The vitamin D metabolites 25-OHD, and 1,25(OH)₂D were analyzed in the laboratory of one of us (L.F.) by high-pressure liquid chromatography and radiochemical assays (15). Osteocalcin was measured by
radioimmunoassay (16) in the laboratory of Dr. Caren Gundberg, Yale University.

Bone Mineral Content

We measured BMC at the distal 1/3 radius in the nondominant arm with a single photon absorptiometer (Model 278A, Norland Corp., Fort Atkinson, WS, U.S.A.). With this technique the error for both accuracy and precision at the distal 1/3 site in adults is less than 3% (17). The BMC, bone width, and BMC/BW ratios of the subjects were compared with the only available age- and height-related population standards, based on data from children living in Wisconsin (18), assessed by single photon densitometry (Norland Corp.).

Statistical Methods

Comparative analysis of initial and follow-up measurements was conducted by a repeated measures two-way analysis of variance using the SASPC (Statistical Analysis Systems, Cary, NC, U.S.A.) program for general linear models. All results are reported as means ± SD. Comparison of the observed BMC/BW with the reference population was computed as a proportion of reference or Z score to provide a single Z-score value that would be comparable at all ages.

RESULTS

Clinical Course and Growth

A description of the study population is provided in Table 1. Most patients were studied within 1 month of diagnosis. Four were studied upon referral after 1–3 years of ineffectual treatment. Patients remained relatively healthy with an average CDAI of 63.4 ± 35 at 1 year and 50.5 ± 37 at 2 years following first study (clinical remission determined by CDAI <150). During 2 years of study, nine patients required treatment with sustained low-dose alternate-day prednisone and eight did not. The average weight and linear growth velocities over this period were similar in both groups (Table 1). None received antimetabolites; three required surgery for obstructive symptoms, all from the non-ADP group.

![Image of bone mineral content graph]

**FIG. 1.** Serial bone density measurements of one-third distal radius in boys with Crohn’s disease compared with reference values for age and height at baseline (n = 17), 1 year (n = 17) and 2 years posttherapy (n = 17). Asterisk indicates boys with Crohn’s disease had lower BMC/BW compared with age-matched (p < 0.0001) or height-matched (p < 0.04) normal values (18) at each measurement point. Cross-hatched bars represent boys with CD, open bars represent height-matched normals, and striped bars indicate age-matched normals.
proved similarly over the 1- and two-year observation periods ($p = 0.0001$) in groups treated with or without ADP as shown in Fig. 2. Z scores for BMD were more negative in the ADP group at baseline (−4.15 vs. −0.14). By 2 years of treatment Z scores were similar between treatment groups (−1.76 vs. −1.44 for ADP and non-ADP groups, respectively) although still well below the mean value for age.

Biochemical and Hormonal Status

Serum total calcium (2.31 ± 0.11 vs. 2.32 ± 0.11 mmol/L), ionized calcium (1.20 ± 0.06 vs. 1.21 ± 0.05 mM), and phosphorus (1.38 ± 0.24 vs. 1.34 ± 0.23 mM) were within the normal range in both ADP and non-ADP groups, respectively, and did not change throughout the study. Serum magnesium decreased significantly over time (0.86 ± 0.06 vs. 0.79 ± 0.06 mM; $p = 0.001$) across groups but remained within the normal range (0.77–0.90 mM) for children 3–14 years in our institution (19) and was not different between treatment groups. Urinary magnesium excretion was low normal at diagnosis and remained unchanged over the three measures (Fig. 3). Hypercalciuria was noted at baseline but declined significantly to normal levels in both groups over the first year ($p = 0.05$) (Fig. 3). Urinary phosphorus remained unchanged (Fig. 3). Serum alkaline phosphatase increased significantly from baseline values ($p = 0.03$) and serum PTH increased over 2 years ($p = 0.001$), but all values were within normal ranges. Average plasma osteocalcin levels did not differ between drug treatment groups and were within the normal range [10–40 ng/ml (20)] at all time points but there was a large degree of variability. Initially, 56% of subjects had osteocalcin levels below the normal range. Osteocalcin values below the normal range at years 1 and 2 occurred in 68% of subjects. There was no correlation between plasma osteocalcin and Tanner stage which could explain the observed wide variability in plasma osteocalcin levels. Mean values for plasma 25(OH)D and 1,25(OH)₂D levels were within normal ranges (5–50 ng/ml and 20–65 pg/ml, respectively). In the non-ADP group, 1,25(OH)₂D levels increased significantly 1 year after baseline ($p = 0.03$). Blood was not available for these measurements at year 2.

Correlation analysis between independent biochemical measures across groups showed no significant association between plasma 1,25(OH)₂D and calcium, magnesium, or osteocalcin nor between serum alkaline phosphatase and osteocalcin.

DISCUSSION

Children with CD have multiple interrelated risk factors that may impact on bone and mineral metabolism. The treatment of CD in children is also complicated by the nutritional and metabolic demands of growth, especially during adolescence. In previous reports (2,4) growth failure defined by var-

![Fig. 2](image-url)  
**FIG. 2.** Bone density measurements of one-third distal radius in boys with Crohn's disease at baseline ($n = 17$), 1 year ($n = 17$) and 2 years ($n = 17$) comparing ADP and non-ADP patients. Asterisk indicates that bone mass increased significantly ($p < 0.001$) over 2 years (by ANOVA), but no difference was observed between prednisone treatment groups. Unbroken line represents prednisone patients; broken line represents non-ADP patients.

![Fig. 3](image-url)  
**FIG. 3.** Urinary creatinine ratio (mmol/mmol) for calcium, phosphorus, and magnesium in boys with Crohn's disease at baseline ($n = 16$), 1 year ($n = 14–17$), and 2 years ($n = 15$) comparing ADP and non-ADP-treated groups with the range of normal expected values. Asterisk indicates that urinary calcium excretion decreased significantly over time ($p < 0.05$) by ANOVA. Unbroken line represents ADP patients; broken line represents non-ADP patients.
ious methods occurred in 32-88% of children with CD. Normalization of growth with improved nutritional intake has previously been reported in CD adolescents treated with low-dose alternate-day corticosteroids (11). In the children treated with ADP in this study, weight and linear growth were maintained at comparable rates to those not receiving the drug (Table 1). However, as a group, CD patients started from a lower point and therefore in many cases remained shorter than age-matched standards (14).

Height (21,22) and pubertal stage (23) are thought to be the most important predictors of bone mass in children. Our population had reduced stature for age and pubertal stage was often delayed. This may explain why measures of bone mineral density in both ADP- and non-ADP-treated subjects were lower when compared with an age- and height-related reference population at all points. Alternatively, the reference population of Wisconsin children may be generally larger and with greater bone mass than an Ontario population of children.

The present study suggests that low-dose alternate-day prednisone therapy does not impede bone mineralization in this population. Patients treated with ADP actually had a lower BMC/BW at baseline but showed more improvement than the non-ADP patients over 2 years. Thus, the ADP treatment might have had a positive influence on bone mineralization through improved appetite and nutritional intake over this time period. The normal vitamin D status (as indicated by plasma concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D) and PTH suggest that dietary intake of minerals and vitamin D were adequate. In addition, the rise in plasma alkaline phosphatase during therapy suggests that the bone mineralization process was active in both treatment groups.

Therapeutic glucocorticoid excess is well documented to cause steroid-induced osteoporosis via a number of mechanisms [reviewed in (5)], but this was not demonstrated in our patients receiving low-dose ADP for treatment of Crohn's disease. Our observations of normal 25OHD and 1,25(OH)2D levels supports previous suggestions that glucocorticoids do not act directly on synthesis or catabolism of vitamin D metabolites (24-26). Glucocorticoid therapy has also been associated with hypercalciuria (7,25), which, in association with the steroid-mediated decline in calcium absorption (26), leads to secondary hyperparathyroidism (26-29) and phosphaturia (30). However, none of these bio-

chemical markers of altered calcium/phosphorus metabolism were abnormal in our population during 2 years of therapy. Mild hypercalciurias was seen at baseline, but this improved with general medical support.

A direct bone effect of glucocorticoid is suggested to occur through suppression of osteoblastic bone-forming activity by inhibition of osteoblast precursor maturation (8). Plasma osteocalcin is considered useful in assessing inhibition of osteoblastic activity. In most adult patients receiving glucocorticoids at doses at low as 2.5 mg/day, circulating osteocalcin levels are reduced (5,28,31,32). Our only indirect indication of such a response is the low plasma osteocalcin observed both at baseline and during treatment in some but not all of the subjects and this occurred similarly in the two treatment groups. The observed variability in plasma osteocalcin was not related to pubertal stage which varied widely among our subjects. Plasma osteocalcin values are known to reach as high as 100 ng/ml during puberty (C. Gundberg, personal communication) and this may explain the five values observed which exceeded the normal range.

The major limitation to our interpretation of bone mineral status is that the distal radius is principally derived from cortical bone and may not be as sensitive an area for measurement of glucocorticoid-induced bone loss as areas of trabecular bone such as the lumbar spine, hip, pelvis, or ribs (5,33).

CONCLUSIONS

Chronic low-dose (0.3 mg/kg/day) alternate-day prednisone was not associated with arrest of bone mineralization in adolescent boys with Crohn's disease. Measurements at diagnosis demonstrated the population to be generally stunted and underweight, and with lower bone mass of the distal radius compared with age-matched reference standards. Some of the observed deficit in bone mass could be attributed to delayed pubertal development and growth. Chronic glucocorticoid therapy also did not induce perturbations in mineral metabolism as indicated by normal urinary calcium, serum PTH, and plasma vitamin D metabolites. The ADP therapy supported growth in bone mass in a manner similar to the Crohn's disease subjects not receiving chronic steroid therapy. Further randomized controlled trials using measures of trabecular bone (34) will be required to confirm the safety and efficacy of low-
dose alternate-day prednisone for chronic treatment of Crohn's disease.

Acknowledgment: The authors gratefully acknowledge the generous contribution of Dr. Caren Gundberg, Department of Orthopedics, Yale University School of Medicine for analysis of the plasma osteocalcin. The technical assistance of Debra Fratant, B.Sc. is gratefully acknowledged. Data collection and organization were done by Martha Davidson, Geri Kraus, and Sally Greenway. Secretarial assistance was provided by Paul Haslett and Arlene Lang. This work was supported in part by the Intestinal Disease Research Program, McMaster University. Dr. Stephanie Atkinson held a Career Scientist Award at McMaster University, supported by the Ministry of Health of Ontario during the conduct of this research.

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