Published in final edited form as:

Osteoporos Int. 2014 July ; 25(7): 1875–1883. doi:10.1007/s00198-014-2701-x.

Changes in trabecular bone density in incident pediatric Crohn's disease: a comparison of imaging methods

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Abstract

Summary—This study of changes in dual energy x-ray absorptiometry (DXA) spine BMD following diagnosis and treatment for childhood Crohn's disease demonstrated that changes in

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Conflicts of interest None.

conventional posteroanterior BMD results were confounded by impaired growth, and suggested that lateral spine measurements and strategies to estimate volumetric BMD were more sensitive to disease and treatment effects.

Introduction—We previously reported significant increases in peripheral quantitative CT (pQCT) measures of trabecular volumetric bone mineral density (vBMD) following diagnosis and treatment of pediatric Crohn's disease (CD). The objective of this study was to compare pQCT trabecular vBMD and three DXA measures of spine BMD in this cohort: (1) conventional posteroanterior BMD (PA-BMD), (2) PA-BMD adjusted for height Z (PA-BMD_{HtZ}), and (3) width-adjusted volumetric BMD (WA-BMD) estimated from PA and lateral scans.

Methods—Spine DXA [lumbar (L1–4) for posteroanterior and L3 for lateral] and tibia pQCT scans were obtained in 65 CD subjects (ages 7–18 years) at diagnosis and 12 months later. BMD results were converted to sex, race, and age-specific Z-scores based on reference data in >650 children (ages 5–21 years). Multivariable linear regression models identified factors associated with BMD Z-scores.

Results—At CD diagnosis, all BMD Z-scores were lower compared with the reference children (all p values <0.01). The pQCT vBMD Z-scores (-1.46 ± 1.30) were lower compared with DXA PA-BMD (-0.75 ± 0.98), PA-BMD_{HtZ} (-0.53 ± 0.87), and WA-BMD (-0.61 ± 1.10) among CD participants. Only PA-BMD Z-scores were correlated with height Z-scores at baseline ($R=0.47$, $p<0.0001$). pQCT and WA-BMD Z-scores increased significantly over 12 months to -1.04 ± 1.26 and -0.20 ± 1.14 , respectively. Changes in all four BMD Z-scores were positively associated with changes in height Z-scores ($p<0.05$). Glucocorticoid doses were inversely associated with changes in WA-BMD ($p<0.01$) only.

Conclusions—Conventional and height Z-score-adjusted PA DXA methods did not demonstrate the significant increases in trabecular vBMD noted on pQCT and WA-BMD scans. WA-BMD captured glucocorticoid effects, potentially due to isolation of the vertebral body on the lateral projection. Future studies are needed to identify the BMD measure that provides greatest fracture discrimination in CD.

Keywords

Bone disease; Crohn's disease; DXA; Glucocorticoids; Growth; Inflammation

Introduction

Children with Crohn's disease have multiple risk factors for impaired bone accrual, including poor growth, delayed maturation, malnutrition, cachexia, elevations in inflammatory cytokines, and glucocorticoid therapy [1, 2]. Inflammatory cytokines, such as tumor necrosis factor α (TNF- α) and glucocorticoids impair bone formation [3, 4] and result in preferential trabecular bone loss [5, 6]. A recent histomorphometry study in adults with quiescent Crohn's disease demonstrated significant reductions in trabecular bone volume [7]. The growing skeleton in children with Crohn's disease may be particularly vulnerable to these detrimental effects. Accordingly, the International Society of Clinical Densitometry (ISCD) Pediatric Official Positions concluded that children with Crohn's disease should

undergo dual energy x-ray absorptiometry (DXA) assessment of lumbar spine bone mineral density (BMD) at diagnosis, and annually thereafter, as indicated [8].

The vast majority of prior pediatric studies of BMD in Crohn's disease relied on DXA [9–15]. DXA is a projection technique that summarizes total bone mass within the projected bone area, resulting in two important limitations. First, trabecular and cortical bone mineral content (BMC) are superimposed, potentially concealing distinct disease and treatment effects on these components of BMC [16]. Second, DXA provides a two-dimensional measure of areal BMD (g/cm^2) that systematically underestimates volumetric BMD (g/cm^3) in children with poor growth [17]. Accordingly, a low areal BMD for age Z-score in the context of short stature in Crohn's disease may be due to smaller bone size relative to age [18]. This effect is well-recognized, and the ISCD report concluded that spine areal BMD results should be “adjusted for absolute height or height age, or compared to pediatric reference data that provide age-, sex-, and height-specific Z-scores” [19]. However, each of these approaches will result in the comparison of children with Crohn's disease to reference children of similar height who are likely younger and less physically mature. This effect was demonstrated by Zemel et al., along with a proposed method to adjust areal BMD for height Z-score (BMD_{HtZ}) that eliminated this bias in healthy children [17]. An alternative approach is to use paired posteroanterior (PA) and lateral DXA spine scans to estimate volumetric “width-adjusted” BMD (WA-BMD, g/cm^3) [20]. This method has the additional advantage of capturing vertebral BMC on the lateral projection, excluding the posterior cortical spinous processes. A recent cross-sectional study in children with juvenile idiopathic arthritis suggested this approach is more sensitive to disease effects in children because it selectively measures the trabecular rich vertebral body and is independent of growth-related increases in BMC of the dense spinous processes [21].

Peripheral quantitative computed tomography (pQCT) provides three-dimensional estimates of cortical and trabecular volumetric BMD and geometry in the appendicular skeleton that are highly correlated with fracture load [22]. We recently reported that Crohn's disease was associated with marked reductions in pQCT measures of trabecular volumetric BMD and cortical dimensions at diagnosis [23]. The trabecular volumetric bone mineral density (vBMD) improved significantly; however, deficits in cortical dimensions progressed.

The objective of this study was to compare pQCT measures of trabecular BMD and DXA measures of posteroanterior BMD (PA-BMD), PA-BMD adjusted for height Z ($\text{PA-BMD}_{\text{HtZ}}$), and WA-BMD in this incident cohort. We aimed to identify anthropometric and disease-related factors associated with changes in these parameters over the first year following diagnosis and treatment of Crohn's Disease. The ability of pQCT and DXA WA-BMD to measure trabecular bone, lead us to hypothesize that pQCT and DXA WA-BMD measures would provide superior estimates of treatment effects on trabecular BMD compared to conventional DXA PA scans.

Methods

Study subjects

Children and adolescents aged 5–21 years with incident Crohn's disease were eligible and were recruited from the Inflammatory Bowel Diseases Center of the Children's Hospital of Philadelphia and gastroenterologists in the community. Baseline study visits were completed within 2 weeks of diagnosis, and follow-up visits were completed 6 and 12 months later. A total of 78 subjects enrolled. Changes in DXA measures of body composition and pQCT measures of bone density and structure were recently described in this cohort [2, 23]. This analysis is limited to the 65 participants with complete spine DXA and tibia pQCT data at the baseline and 12-month visit. Age, sex, and baseline Pediatric Crohn's Disease Activity Index (PCDAI) score did not differ significantly between the two groups; however, the BMI, height, PA-BMD, WA-BMD, and tibia trabecular BMD Z-scores were significantly higher among the participants that did not return for the 12-month visits.

The reference population was a cross-sectional sample of healthy children and adolescents from the greater Philadelphia area, as previously described [24]. Reference subjects were excluded for a history of illnesses or medications that may affect growth or nutritional status. Scanning protocols in the controls were modified over the study interval. Therefore, pQCT measures of trabecular vBMD and DXA measures of PA and WA-BMD were available using the same scan protocols for comparison with the Crohn's disease subjects in 652, 829, and 802 controls, respectively. The reference participants ranged from 5 to 21 years of age with a mean of 11.8 and SD of 3.9 years. The sample was 48 % male and 44 % black race. The mean $\pm$ SD height and BMI Z-scores were 0.27 ± 0.92 and 0.36 ± 1.02 , respectively.

The study protocol was approved by the Institutional Review Board at the Children's Hospital of Philadelphia. Informed consent was obtained from young adult subjects and the parents or guardians of subjects under the age of 18 years. Assent was obtained from subjects between 7 and 18 years of age. All study methods and procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki.

Crohn's disease characteristics and definitions

Crohn's disease activity was assessed using the PCDAI based on symptoms (30 %), physical examination (30 %), laboratory parameters (20 %), and growth data (20 %), with scores ranging from 0 to 100 [25]. We classified participants into three categories; no disease (<10), mild disease (11–30), and moderate/severe disease (>30). Medical charts were reviewed, and participants were interviewed for date of diagnosis, prior therapies, symptom duration prior to diagnosis, extraintestinal manifestations, and current medications. Participants were provided with glucocorticoid diaries at the baseline visit; and the diaries were compared with the medical record at 6 and 12 months. Intravenous methylprednisolone doses were converted to prednisone equivalents, and the cumulative glucocorticoid exposure (mg/kg) in each subject was summarized over the 12-month interval.

Anthropometry and pubertal development

Weight and height were measured using a digital scale to the nearest 0.1 kg (Scaltronix, White Plains, NY) and a stadiometer to the nearest 0.1 cm (Holtain Ltd., Crosswell, Crymch, UK), respectively. Pubertal status was assessed with a validated self-assessment questionnaire [26] and classified according the method of Tanner [27].

Spine DXA and tibia pQCT scans

Bone measures in the left tibia were obtained by pQCT using a Stratec XCT2000 device (Orthometrix, White Plains, NY) with a 12-detector unit, voxel size of 0.4 mm, slice thickness of 2.3 mm, and scan speed of 25 mm/s. Scans were analyzed with Stratec software version 5.50, using contour mode 1 and peel mode 4 with inner and outer thresholds of 200 and 600 mg/cm³, respectively. A scout view was obtained to place the reference line at the proximal border of the distal tibia growth plate, and trabecular BMD (mg/cm³) was measured at the 3 % distal metaphysis site. The manufacturer's hydroxyapatite phantom was scanned daily for quality assurance. The coefficient of variation (CV) for trabecular vBMD was 1.4 % in children and adolescents based on data from our institution.

DXA scans of the spine were performed using a Delphi/Discovery (Hologic, Bedford, MA) densitometer with a fan beam in the array mode, and analyzed with software version 12.3. DXA scans of the PA (L1–4), PA (L3), and lateral lumbar spine (L2–4) were obtained using standardized positioning techniques in the supine position. Lateral images were obtained with the rotating C-arm device. Measures of areal BMD (g/cm²) were derived from the PA scan of L1–4 and L3. Due to rib interference with L2 in 37 % and iliac crest interference with L4 in 21 % of reference participants on the lateral scans, the lateral scan results were limited to L3. The proportions with interference were comparable to reports in adults [28]. Paired PA-lateral DXA scans of lumbar vertebrae L3 were used to derive WA-BMD (g/cm³) [20]. This technique incorporates the vertebral dimensions on the PA and lateral scans to estimate vertebral volume assuming an elliptical shape. Vertebral body BMC is measured on the lateral scan, thereby excluding the cortical spinous processes, and is divided by the estimate of vertebral volume to generate WA-BMD.

PA spine scans of a lumbar spine phantom were performed daily. In our institution, the in vitro CV for PA spine scans was less than 0.6 % and the in vivo CV in adults was 1.0 %. Precision data for the lateral spine are not available in children. However, the precision for isolated lateral spine and WA-BMD measures obtained using the DXA rotating C-arm device have been described in adults [28]. The precision for WA-BMD measures obtained in L2–4 was 1.5 %. Precision estimates for WA-BMD were not provided for individual vertebra. However, the precision for isolated lateral BMD was greater for L3 at 1.8 %, compared with L2 (2.6 %) and L4 (2.4 %), and was comparable to the precision for isolated lateral BMD in L2–4 (1.2 %).

Statistical analysis

Analyses were conducted using STATA 10.0 (Stata Corporation, College Station, TX). A two-tailed *p* value of <0.05 was the criterion for statistical significance. Differences in means were assessed using Student's *t* test for normally distributed variables or Wilcoxon's

rank sum test for non-normally distributed variables. Correlations between continuous variables were assessed by Pearson product moment correlations or Spearman rank correlations, where appropriate. Differences in proportions were assessed using the χ^2 test.

Age- and sex-specific Z-scores for height and BMI were calculated using National Center for Health Statistics data [29]. The pQCT and DXA BMD outcomes were converted to sex- and race (black vs. all others)-specific Z-scores relative to age using the method of smooth L curve, mean and coefficient of variation in the reference subjects [30]. The LMS method accounts for the nonlinearity, heteroscedasticity, and skew of bone data in growing children. PA-BMD Z-scores were adjusted for height Z-score to generate PA-BMD_{HtZ} using the method of Zemel et al. [17]: regression equations that adjusted for age, height Z-score, and an age-by-height Z-score interaction were developed in the reference population and applied to the Crohn's disease participants.

Disease activity, growth and nutrition status, and pubertal status may contribute to bone deficits in children and adolescents with Crohn's disease at diagnosis [23]. Therefore, the multivariate regression models for each of the four baseline BMD Z-scores were adjusted for PCDAI, height and BMI z-score, and pubertal status (Tanner 1–2 vs. 3–5). Similarly, the multivariate regression models for changes in each of the four BMD Z-scores over 12 months was adjusted for baseline BMD, height, and BMI Z-scores, change in height and BMI Z-scores, pubertal status at baseline (Tanner 1–2 vs. 3–5), baseline PCDAI, changes in PCDAI, and concurrent glucocorticoid exposure. The total glucocorticoid exposure (mg/kg) over the 12-month interval was categorized as none vs. each tertile of exposure. The models were adjusted for changes in height Z-score to identify associations between improvements in growth status and BMD. This is not accomplished by the BMD_{HtZ} method alone since it only adjusts for confounding effect of short stature at the time of the scan and does not address the potential contribution of growth to recovery of BMD.

The baseline and longitudinal models were developed using automated backward selection procedures for the potential confounders and exposures listed above. At each step, the remaining variable with the biggest *t* test *p* value >0.2 was removed until all variables eligible for removal had *p* values smaller than this criterion. The model coefficient and *p* values were reestimated after each removal. In addition, the associations of individual covariates with changes in the BMD Z-scores were examined in univariate models, and in bivariate models adjusted for the baseline BMD Z-score (when significant). Height and BMI Z-scores were only moderately correlated ($R=0.30$) and tests of the variance inflation factor did not detect evidence of colinearity in the models.

Results

Baseline subject characteristics

Table 1 summarizes subject and disease characteristics in Crohn's disease participants. The predominance of whites and males among the Crohn's disease subjects was consistent with the demographic distribution of the disease [31]. Subjects with Crohn's disease had delayed puberty (assessed as age relative to Tanner stage and sex, $p<0.001$) and significantly lower height and BMI Z-scores at disease diagnosis, compared to reference participants. The

majority of subjects had moderate to severe Crohn's disease activity, growth failure, anemia, and extraintestinal manifestations at diagnosis, as previously described [23].

Baseline BMD deficits

Significant trabecular deficits were observed at the time of diagnosis (Table 2); the pQCT and three DXA BMD Z-scores were significantly lower at Crohn's disease diagnosis, compared with the reference population (all p values <0.001). The mean pQCT vBMD Z-score was significantly lower than each of the DXA BMD Z-scores ($p<0.001$). PA-BMD_{Htz} Z-scores were significantly higher than PA-BMD Z-score, consistent with the effect of adjusting for the low height Z-score in Crohn's disease. The median difference in PA-BMD_{Htz} and PA-BMD Z-scores was 0.27 (range -0.67 to 1.36) at the baseline visit. PA-BMD Z-scores were positively correlated with height Z-scores ($R=0.48$, $p<0.001$); the remaining BMD Z-scores were not significantly associated with height Z-score. All four BMD Z-scores were positively associated with BMI Z-score ($R=0.32 - 0.55$, $p<0.01$).

In multivariate stepwise regression models of baseline results, all four BMD Z-scores were positively and independently associated with BMI Z-score ($\beta=0.36-0.46$; all p -values 0.01). Only PA-BMD Z-score was independently associated with height Z-score ($\beta=0.32$, 95 % C.I. 0.11 , 0.53 , $p<0.01$). Greater PCDAI score was associated with lower pQCT vBMD Z-score ($\beta=-0.02$, 95 % C.I. -0.04 , -0.002 , $p<0.05$). The DXA BMD Z-scores were not associated with PCDAI score (all p values >0.20).

Improvements in disease activity following initiation of therapy

Table 1 illustrates the marked improvement in BMI Z-score, PCDAI, and laboratory parameters following initiation of therapy for Crohn's disease (CD). The proportion of participants with moderate to severe disease decreased from 63 to 2 %; 66 % had no evidence of disease activity by PCDAI score at 12 months. The therapies administered over the study period have been described in detail and included glucocorticoids, immunomodulators (6-mercaptopurine, azathioprine, and methotrexate) and biologics (infliximab) [23]. A total of 24 participants did not receive any glucocorticoid therapy over the study interval. The glucocorticoid diaries were incomplete in three participants. The remaining 38 participants were divided into dose tertiles: the 13 in the first tertile received a mean $\pm$ SD of 0.06 ± 0.03 mg/kg/day, the 13 in the second tertile received a mean of 0.13 ± 0.02 mg/kg/day, and the 12 in the highest tertile received a mean of 0.29 ± 0.11 mg/kg/day over the 12-month interval.

Changes in BMD Z-scores

The changes in the four BMD Z-scores over the 12 months following Crohn's disease diagnosis are summarized in Table 2. PA-BMD and PA-BMD_{Htz} Z-scores did not increase; however, WA-BMD and pQCT vBMD Z-scores improved significantly. Changes in pQCT vBMD Z-scores were moderately correlated with changes in PA-BMD ($R=0.36$, $p<0.01$), PA-BMD_{Htz} ($R=0.33$, $p<0.01$), and WA-BMD ($R=0.42$, $p<0.001$) Z-scores. The correlation of pQCT vBMD Z-scores with WA-BMD Z-scores was not significantly different than the correlations of pQCT BMD Z-scores with PA-BMD or PA-BMD_{Htz} Z-scores.

Changes in height and BMI Z-scores over the 12-month interval are shown in Table 2. Univariate models demonstrated that increases in height Z-score were significantly associated with increases in PA-BMD and PA-BMD_{HtZ} Z-scores (both $p < 0.001$) while disease activity and glucocorticoid exposure were not. In bivariate models adjusted for the baseline BMD Z-score, increases in height Z-score were associated with increases in WA-BMD ($p=0.001$) and pQCT vBMD ($p=0.004$) Z-scores, and greater glucocorticoid tertile was associated with declines in WA-BMD Z-score (second tertile $p<0.05$ and third tertile $p<0.03$, vs. no glucocorticoid exposure). The multivariate stepwise regression models for each of the four BMD Z-scores are shown in Table 3. Greater increases in height Z-scores were positively and independently associated with changes in BMD Z-scores for all four outcomes. No other subject or disease characteristics were associated with changes in PA-BMD or PA-BMD_{HtZ} Z-scores. Changes in pQCT trabecular vBMD Z-scores were significantly and independently associated with changes in BMI Z-scores. There was a significant dose response relationship between greater mean glucocorticoid exposure and lower BMD for WA-BMD Z-score only. When all of the final models were repeated, excluding the baseline covariates (e.g., BMI Z-score), that were significantly associated with the baseline BMD Z-score, the results were unchanged.

In order to compare the PA and WA-BMD methods within the same vertebrae, we repeated the regression models using the 12-month changes in L3 PA-BMD and BMD_{HtZ} as the outcomes. These analyses confirmed all of the results with comparable magnitude and statistical significance observed using L1–4 BMD.

Discussion

This study demonstrated significant deficits in DXA spine areal BMD in children with Crohn's disease at diagnosis, and identified potential strengths and weaknesses of methods to interpret these scans. Two prior studies reported DXA spine BMD results in children and adolescents with incident Crohn's disease, noting significant deficits at baseline and no significant changes following diagnosis. The current study advances previous studies in two important ways. First, these studies were limited by small numbers of controls (less than 50). This limitation is illustrated by the low mean BMD Z-scores in the healthy controls (-0.37 in the study by Sylvester et al., and -0.83 to -0.72 in the study by Gupta et al.) [14, 32]. The robust reference population described here constitutes the largest used in the assessment of Crohn's disease in children or adults, allowing adjustment for age, sex, race, and pubertal maturation. Second, the current study examined the impact of two alternate strategies to assess spine BMD: PA-BMD_{HtZ} and WA-BMD. The first was developed to adjust BMD Z-scores for the confounding effects of poor growth and the second was proposed as a method to estimate volumetric BMD excluding the cortical BMC of the superimposed spinous processes.

Zemel et al. recently published a critical appraisal of methods to adjust BMD Z-scores for poor growth using data in over 1,500 children from the multicenter Bone Mineral Density in Childhood Study, with validation in a separate sample of healthy children [17]. Spine and whole body BMD-for-age Z-scores were compared with Z-scores generated using height-age or height-specific reference data (i.e., BMD relative to height). In addition, adjustment

for height Z-score was proposed as an alternative approach that would simultaneously consider both height and age. These analyses confirmed that use of height-age or the assessment of BMD relative to height resulted in a systematic bias: older healthy children with height Z-scores less than -1.0 had BMD Z-scores greater than expected relative to height or height-age. In contrast, adjustment for height Z-score was the only approach for which the effects of short (or tall) stature were not significant. The publication provides the equations necessary to adjust sex- and age-specific BMC and BMD Z-scores for height Z-score. Therefore, this technique can be readily applied in clinical practice, to assess the degree to which a low BMC or BMD Z-score can be attributed to short stature.

In this study, equations to adjust for height Z-score were developed using the Zemel method within our reference population. This is the first study to employ this strategy in Crohn's disease. This adjustment resulted in a median increase in BMD Z-scores of 1.14 (range 0.81 to 1.35) among the six Crohn's disease participants with height Z-scores <-2.0 . At enrollment, only the unadjusted PA-BMD Z-score was significantly associated with height Z-score, illustrating the confounding effect of short stature on this measure.

While PA-BMD_{HIZ} methods address the confounding effects of poor growth, additional methods are needed to minimize the effect of superimposed cortical bone. The lack of significant increases in PA-BMD and PA-BMD_{HIZ} Z-scores following diagnosis may have been due to concealment of trabecular changes by the superimposed cortical bone. In contrast, WA-BMD isolates the BMC within the vertebral body, excluding the cortical spinous processes. This effect was best illustrated in our study of children with steroid sensitive nephrotic syndrome [33]. Mean pQCT trabecular vBMD Z-scores were significantly lower (-0.60) and cortical vBMD Z-scores were significantly greater ($+1.17$) compared with the reference population. Mean DXA PA-BMD Z-scores were normal (-0.08); however, WA-BMD Z-scores were significantly reduced (-0.45). The significant dose-related association between glucocorticoid exposure and WA-BMD Z-score reported here (Table 3) further supports the use of WA-BMD to assess trabecular bone health. Nonetheless, WA-BMD has important limitations. First, the analyses were limited to single vertebrae (L3) due to rib interference with L2 and iliac crest interference with L4 in a substantial proportion of participants. However, as noted in the "Methods," the precision for lateral BMD of L3 alone was comparable to L2–4. When the analyses were repeated using L3 PA-BMD, the results observed with L1–4 BMD were duplicated. Second, WA-BMD reference data are not widely available. Third, although WA-BMD results exclude cortical bone of the spinous process, the vertebral cortical shell may still affect results by concealing trabecular deficits. This may account for the fact that WA-BMD was not significantly lower in Crohn's disease participants at 12 months, compared with the reference population, despite the marked persistent deficits in pQCT trabecular vBMD.

The significant and positive association observed between increases in height Z-score and the three measures of BMD that were either adjusted for bone size (PA-BMD_{HIZ}) or based on three-dimensional measurements (WA-BMD and vBMD) suggest that disease and treatment characteristics associated with improvements in growth are also associated with improvements in trabecular BMD. In addition, this positive association may have a biologic basis. Numerous prior studies, including a report in Crohn's disease, demonstrated that

children can recover spine BMD and even reconstitute vertebral compression fractures during growth and maturation [34]. Therefore, the positive association with height Z-score observed here across all BMD outcomes may reflect a greater ability to recover trabecular bone during growth.

There are potential explanations for the lack of an association between glucocorticoid exposure and pQCT trabecular vBMD Z-scores. First, trabecular vBMD is highly variable along the length of the tibia metaphysis and changes with growth [35]. A single 2.3-mm slice may not provide adequate precision to detect treatment effects over time. Second, glucocorticoids may have different effects in the axial vs. appendicular skeleton where weight bearing effects differ.

The greatest limitation of the study is the lack of spine QCT data as a gold standard measure of spine trabecular BMD. However, prior studies in adults that included spine QCT scans documented that lateral DXA was superior to PA DXA in its diagnostic sensitivity for vertebral fractures [36], and for the detection of bone loss in the setting of glucocorticoid therapy [37]. The consistent finding of improvements in appendicular and axial trabecular BMD using DXA and pQCT, respectively, in the setting of improvement in disease activity provides strong evidence of true improvements in trabecular bone health in this Crohn's disease cohort. Additionally, the fact that the WA-BMD approach demonstrated a significant dose response for glucocorticoid exposure speaks to the clinical validity of this approach. An additional limitation is the lack of lateral thoracolumbar spine films to determine if vertebral compression fractures were present at baseline or follow-up. A recent cross-sectional study in 27 pediatric patients with Crohn's disease reported vertebral fractures in three participants [38]. DXA PA spine BMD, disease activity and prednisolone dose were not associated with fractures. Last, given that the participants that did not return for the 12-month visit had greater height, BMI, and BMD Z-scores at baseline, these results may not be generalizable to children with less severe growth failure, malnutrition, or bone deficits.

We recently reported changes in DXA spine PA-BMD and pQCT trabecular BMD Z-scores following renal transplantation in children [39]. The transplant recipients were treated with high-dose glucocorticoids and experienced marked reductions in both DXA spine PA-BMD and pQCT trabecular BMD Z-scores. Greater glucocorticoid exposure was significantly associated with greater declines in DXA and pQCT Z-scores. These data suggest that pQCT trabecular BMD and conventional DXA PA-BMD methods may be sensitive to glucocorticoid effects in the setting of high dose and sustained exposure while WA-BMD methods were needed to detect the impact of lesser glucocorticoid exposure in Crohn's disease. This is consistent with a prior adult study suggesting the lateral projection was more sensitive than the PA projection for detecting mild vertebral compression fractures [36].

Low DXA BMD and pQCT vBMD are contributing factor for fractures in healthy children [40, 41]; however, the relations between DXA BMD and fracture risk in children with chronic illness may be different than those observed in healthy children and have not been adequately characterized. In a small series of 32 children with chronic disease, vertebral compression fractures were poorly predicted by spine PA-BMD measurements [42]. In contrast, a prospective cohort study of 118 children treated with glucocorticoids reported

that DXA PA spine areal BMD Z-scores were lower in children with incident vertebral fractures [43]. To our knowledge, no studies have employed quantitative data using receiver operating characteristic curves or other measures of diagnostic test characteristics (such as the sensitivity and specificity) to assess the ability of varied DXA sites and analytic strategies to discriminate between children with and without a fracture in chronic disease. Additional studies are imperative in order to identify the best analytic approach to the interpretation of DXA data for research and clinical applications.

Conclusions

This comparison of pQCT measures of trabecular BMD and three different DXA measures of spine BMD revealed important differences in the associations with anthropometric and disease-related factors. For example, changes in height Z-scores strongly confounded changes in conventional DXA spine BMD for age Z-scores in this cohort. These data also suggest that PA measures of spine BMD may not capture disease and treatment effects on trabecular bone. This has important implications given the recent ISCD recommendation that clinicians assess DXA spine BMD in children with Crohn's disease, and other systemic inflammatory diseases, at diagnosis, and annual thereafter, as clinically indicated [8].

Acknowledgments

We greatly thank the children and their families who participated in this study for their dedication and the physicians and nurses in the Division of Gastroenterology at the Children's Hospital of Philadelphia. This project was supported by grants R01-DK060030, K24-DK076808, and UL1-RR-024134 from the National Center for Research Resources. Dr. Berkenstock was supported by the Society of Pediatric Research, Dr. Tsampalieros by the University of Ottawa, Faculty of Medicine, and Dr. Griffin by the Doris Duke Clinical Research Foundation.

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Table 1Crohn's disease characteristics (*n*=65)

Variable	Value at baseline	Value at 12 months
Age at diagnosis (yr), mean (SD)	12.7±2.5	
Range	(7.7 to 17.6)	
Sex, % male	54	–
Race, % black	6	–
Tanner stage 1–2, %	55	29
Height Z-score, mean ± SD	−0.35±1.04	−0.35±1.00
BMI Z-score, mean ± SD	−0.67±1.00	−0.14±0.90
PCDAI score, median (range)	38 (5 to 30)	8 (0 to 40)
PCDAI disease severity, <i>n</i> (%)		
No active disease (10)	2 (3 %)	43 (66 %)
Mild (11–30)	22 (34 %)	20 (31 %)
Moderate/severe (>30)	40 (63 %)	1 (2 %)
Albumin (g/dL), median (range)	3.5 (1.8 to 4.7)	4.0 (3.1 to 4.9)
ESR (mm/h), median (range)	24 (0 to 128)	17 (0 to 60)
Anemia, <i>n</i> (%)	45 (71 %)	21 (34 %)
Site of disease, <i>n</i> (%)		
Upper GI tract disease ^a	57 (88 %)	–
Isolated upper GI tract disease	4 (6 %)	–
Colonic disease	60 (92 %)	–
Isolated colonic disease	5 (8 %)	–
Perianal involvement	26 (40 %)	–

This table is limited to the 65 participants included in this study. Data are presented as mean ± SD for normal distribution, or median (range) for skewed, or *n* (%). This score was incomplete in one participant

PCDAI Pediatric Crohn's disease Activity Index, ESR erythrocyte sedimentation rate, GI gastrointestinal

^aUpper GI tract disease defined as proximal to the colon and including the terminal ileum

Table 2

Baseline and 12-month anthropometry and BMD Z-scores

Z-score	Baseline	12 Months	Change <i>p</i> value ^a
Height	-0.35±1.04 -0.48 (-0.81, 0.25)	-0.35±1.00 -0.33 (-0.99, 0.30)	0.97
BMI	-0.67±1.00 -0.81 (-1.37, -0.04)	-0.14±0.90 -0.14 (-0.81, 0.44)	< 0.0001
DXA PA-BMD	-0.75±0.98 -0.92 (-1.33, 0.02)	-0.84±1.06 -0.86 (-1.56, -0.22)	0.27
DXA PA-BMD _{HIZ}	-0.53±0.87 -0.62 (-1.11, -0.04)	-0.60±0.99 -0.76 (-1.31, -0.005)	0.21
DXA WA-BMD	-0.61±1.10 -0.72 (-1.16, -0.11)	-0.19±1.22 -0.33 (-0.82, 0.32)	< 0.01
pQCT BMD	-1.46±1.30 -1.51 (-2.16, -0.66)	-1.05±1.26 -1.05 (-1.68, -0.15)	0.0001

Z-scores are expressed as means ± SD and median [Interquartile Range (IQR)]. All baseline BMD Z-scores are significantly lower compared with the reference population ($p<0.001$). All 12-month BMD Z-scores are significantly lower compared with the reference population ($p<0.001$) with the exception of DXA WA-BMD Z-scores which did not differ from the reference population ($p=0.20$)

^a Change *p* value represents a difference from baseline within the Crohn's group as tested by paired *t* test

Table 3
Multivariable linear regression models of changes () in Z-scores from baseline to 12 months

	PA-BMD β (95 % CI)	PA-BMD _{HIZ} β (95 % CI)	WA-BMD β (95 % CI)	Trab-BMD β (95 % CI)
Baseline Z	0.16 (0.04, 0.28) ^b	0.14 (0.01, 0.28) ^a	-0.48 (-0.75, -0.22) ^c	-0.17 (-0.32, -0.03) ^a
Prepubertal	-	-	-	0.42 (-0.03, 0.88)
Height Z	-	-	-0.23 (-0.50, 0.05)	-
BMI Z-score				
Baseline	1.29 (0.94, 1.63) ^c	0.78 (0.44, 1.11) ^c	0.90 (0.02, 1.78) ^a	1.03 (0.45, 1.61) ^c
Change	-	-	0.36 (0.01, 0.70) ^a	0.27 (0.04, 0.51) ^c
PCDAI	-	-	-	0.33 (0.02, 0.64) ^c
Glucocorticoid exposure (total mg/kg) vs. none	-	-	0.01 (-0.005, 0.03)	-
1 st Tertile	-	-	-	-0.008 (-0.02, 0.003)
2 nd Tertile	-	-	-0.50 (-1.26, 0.27)	-
3 rd Tertile	-	-	-0.76 (-1.46, -0.05) ^a	-
Adjusted R ²	0.52	0.30	-1.13 (-2.00, -0.25) ^b	-
Mean VIF	1.23	1.10	0.47	0.40
			1.47	1.25

A forward stepwise regression model was constructed with the covariates shown here. Results that were included in the Table that were not statistically significant (i.e., $p < 0.05$) had a p value < 0.2 , per the stepwise criteria. Whereas the dashes (-) represent covariates that were excluded in the final model following stepwise criteria

VIF Variance Inflation Factor

^a 0.05

^b 0.01

^c 0.001