Published in final edited form as:

Bone. 2018 July ; 112: 128–135. doi:10.1016/j.bone.2018.04.012.

Changes in Pediatric DXA Measures of Musculoskeletal Outcomes and Correlation with Quantitative CT Following Treatment of Acute Lymphoblastic Leukemia

Sogol Mostoufi-Moab, MD, MSCE¹, Andrea Kelly, MD, MSCE¹, Jonathan A. Mitchell, PhD¹, Joshua Baker, MD, MSCE², Babette S. Zemel, PhD¹, Jill Brodsky, MD³, Jin Long, PhD⁴, and Mary B. Leonard, MD, MSCE¹

¹Department of Pediatrics, The Children's Hospital of Philadelphia, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104

²Department of Medicine, Perelman School of Medicine, The University of Pennsylvania Perelman School of Medicine, Philadelphia, PA 19104

³Care-Mount Medical, Poughkeepsie, NY 12601

⁴Department of Pediatrics, Stanford University School of Medicine, Palo Alto, CA

Abstract

We previously reported significant gains in pQCT measures of tibia trabecular bone mineral density (BMD) and cortical structure following completion of therapy in children and adolescents with acute lymphoblastic leukemia (ALL). The objective of this study was to examine changes in DXA measures used in clinical practice and expressed as Z-scores using robust national reference data. Children and adolescents, ages 5 to 18 years were enrolled within 2 (median 0.8) years of completing ALL therapy. DXA total-body less-head bone mineral content (TBLH-BMC), and spine, total hip, femoral neck, and 1/3rd radius areal BMD (aBMD) were assessed in 45 participants at enrollment and 12-months later. Linear regression models examined correlates of changes in DXA Z-scores. Changes in DXA outcomes were compared to changes in tibia pQCT trabecular and cortical volumetric BMD (vBMD) and cortical area. At enrollment, DXA TBLH-BMC, spine and radius aBMD Z-scores were not significantly reduced in ALL survivors; however, total hip [median −0.74 (IQ range −1.51 to −0.04)] and femoral neck [−0.51 (−1.24 to 0.14)] aBMD Z-scores were lower (both $p < 0.01$) compared to reference data. DXA Z-scores at all skeletal sites increased over 12 months. Despite improvement, total hip Z-score remained lower at −0.55 (−1.05 to 0.18). The increases in TBLH-BMC, total hip and femoral neck aBMD Z-scores were more pronounced in those enrolled within 6 months of completing ALL therapy, compared to those enrolled at >6 months. Gains in TBLH-BMC, total hip, femoral neck and radius aBMD Z-

Corresponding author: Sogol Mostoufi-Moab, MD, MSCE, The Children's Hospital of Philadelphia, 2716 South Street; 14th Floor, Philadelphia, PA 19146, Phone: 267 426-9725, Fax: 267 425-1075, moab@email.chop.edu.

Disclosure: All authors disclose no potential conflicts of interest.

Authorship: S.M.M. and M.B.L. designed the study; S.M.M., J.B., and J.L. collected and assembled the data; S.M.M., M.B.L., A.K., B.S.Z. and J.L. analyzed data and performed statistical analysis; S.M.M., M.B.L., A.K., J.L., J.B., J.M. and B.S.Z. interpreted the results; S.M.M. and M.B.L. wrote the paper; S.M.M., A.K., J.M., J.B., J.L., B.S.Z., and M.B.L. reviewed and critiqued the manuscript and contributed to revisions. All authors approved the final manuscript.

scores were significantly associated with gains in tibia cortical area Z-scores ($R=0.56$ to 0.67 , $p < 0.001$). Changes in TBLH and proximal femur sites were associated with gains in trabecular vBMD Z-scores ($R=0.37$ to 0.40 ; $p < 0.01$); these associations were not significant when adjusted for gains in cortical area. In summary, gains in DXA measures were most pronounced in total hip and femoral neck following ALL therapy. The gains in all DXA measures, with the exception of lumbar spine, reflected gains in cortical area. Overall, ALL survivors demonstrate skeletal recovery following completion of therapy; a small sub-group continue to demonstrate deficits and benefit from continued observation to ensure improvement over time.

Keywords

acute lymphoblastic leukemia; bone mineral content; bone mineral density; dual-energy X-ray absorptiometry; and cortical dimensions

1. INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy and current survival rates now exceed 80%.[1] Unfortunately, ALL is associated with substantial skeletal morbidity, including fractures, osteonecrosis, and bone pain during therapy.[2] The landmark multicenter Steroid-associated Osteoporosis in Pediatric Population (STOPP) study enrolled children and adolescents at the time of ALL diagnosis and documented a cumulative incidence of vertebral fractures of 26% over the subsequent four years.[3] Greater glucocorticoid exposure, prevalent vertebral fractures and lower DXA spine aBMD Z-scores were associated with incident fractures; each unit lower spine aBMD Z-score was independently associated with a 60% greater risk of incident vertebral fractures.[4] While this study provided important insights into skeletal morbidity in childhood ALL, the DXA measures were limited to the spine. Given the potential limitations of spine DXA in children, [5, 6] studies that assess bone health at additional sites are necessary.[7]

Clinical practice guidelines recommend DXA as part of comprehensive bone health assessment after childhood cancer therapy.[8] However, the optimal DXA site for identifying bone deficits and skeletal recovery after chemotherapy in children has not been addressed. Studies of bone health in childhood chronic diseases benefited significantly from the development of robust national reference data for multiple skeletal sites through the NIH funded Bone Mineral Density in Childhood Study (BMDCS), including prediction equations to adjust for height.[9]

We recently reported marked gains in the peripheral quantitative CT (pQCT) measures of tibia trabecular volumetric BMD (vBMD) and cortical cross-sectional area (with transient decreases in cortical vBMD) in children and adolescents following completion of ALL therapy without cranial radiation.[10] The objective of this study was to examine changes at multiple DXA sites (total body less-head, lumbar spine, total hip, femoral neck, and distal 1/3rd radius) in this cohort, to examine correlates of gains in DXA bone outcomes, and to determine which DXA measures best reflect the gains previously identified using pQCT.

2. MATERIALS AND METHODS

2.1 Study participants

This prospective study included children and adolescents, ages 5-18 years, diagnosed with ALL and treated at the Children's Hospital of Philadelphia (CHOP) as previously described. [10] Study participants were eligible if in complete remission and excluded if treated with cranial radiation or diagnosed with second malignancy or Down syndrome. Patients with cranial radiation were excluded to avoid confounding of skeletal measures by radiation-related neuroendocrine deficits such as growth hormone deficiency or hypogonadism. Enrollment study visits were completed within two years after completion of maintenance chemotherapy with a subsequent 12-month follow up study visit. We enrolled 50 of the total 86 eligible patients contacted (58%). Patient demographics and ALL disease characteristics were not different between eligible participants who enrolled and those who declined participation. The study protocol was approved by the CHOP Institutional Review Board. Participant assent along with parental consent was obtained from all study participants.

2.2 Anthropometry and physical maturity

Height was measured with a stadiometer (Holtain, Crymch, UK) and weight with a digital scale (Scaletronix, White Plains, NY). Pubertal development in ALL participants was classified according to the method of Tanner by a pediatric endocrinologist (S.M.M).[11]

2.3 ALL disease and treatment characteristics

Participants were treated as per the Children's Oncology Group Consortium protocols. Medical charts were reviewed for date of diagnosis, leukemia risk group (standard vs. high risk),[12] duration of chemotherapy, and time since therapy completion. Cumulative (grams per square meter) glucocorticoid (prednisone and/or dexamethasone), methotrexate and 6-mercaptopurine exposure over the treatment interval were determined. Medical (including endocrine abnormalities) and fracture history were reviewed at each visit.

2.4 ALL fracture data

ALL participant fracture summary was captured based on retrospective data given occurrence at the time of leukemia diagnosis and/or during chemotherapy, prior to enrollment for this study. All non-vertebral (excluding hands and feet) fractures reported were radiographically confirmed by a certified radiologist. Vertebral fractures were diagnosed on lateral spine radiograph following presentation of back pain at the time of ALL diagnosis, and the decision for imaging at the discretion of the treating oncologist. Identified vertebral fractures were graded according to the Genant method as mild (grade 1), moderate (grade 2), or severe (grade 3).[13]

2.5 Dual energy X-ray absorptiometry

DXA scans of the posterior anterior lumbar spine (L1-L4), total body less-head (TBLH), non-dominant forearm, and left hip were performed (Hologic, Bedford, MA) in the array mode and analyzed using software versions 12.3 and 12.4 to generate areal BMD (g/cm^2) and BMC (g). Spine phantoms were scanned daily and total-body phantoms were scanned

weekly. The precision error for aBMD and BMC was less than 1% for the spine, and less than 2.5% for the total-body phantoms, respectively.

DXA measures of leg lean mass (kg) were obtained from the total body scan as an index of skeletal muscle in order to assess the longitudinal relationship between muscle and bone “i.e. the functional muscle-bone unit.” It is our practice to use leg lean mass, as opposed to total body lean mass, for three reasons. First, appendicular lean mass is the international standard for assessment of sarcopenia in adults.[14] Second, we previously demonstrated that leg lean mass was associated with cardiorespiratory fitness in children with congenital heart disease while total body lean mass was not.[15] Third, we also demonstrated that total body lean mass underestimated muscle deficits in childhood cancer survivors due to altered body proportions (longer legs relative to height) following spine radiation.[16]

2.6 Tibia pQCT Assessment

Tibia pQCT scans were obtained at 3 and 38% of the tibia length proximal to the distal growth plate, as previously described.[10] Trabecular vBMD (mg/cm^3) was assessed at the 3% metaphyseal site, and cortical vBMD and dimensions [periosteal and endosteal circumference (mm), cortical cross-sectional area (CSA, mm^2)] at the 38% diaphyseal sites. The manufacturer’s hydroxyapatite phantom was scanned daily. In our laboratory, the coefficient of variation (CV) for short-term precision ranged from 0.5% to 1.6% for pQCT outcomes in children and young adults.[10]

2.7 Statistical Analysis

Statistical analysis was performed using STATA 14.0 (Stata Corp, College Station, TX). A P-value of <0.05 was considered statistically significant, and two-sided tests of hypotheses were used throughout. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range) for skewed distributions. Group differences between ALL tested using the Student participants and the published BMDCS reference data were ’s single sample t-test. Correlations between continuous variables within the ALL participants were assessed by Pearson or Spearman’s rank correlations, where appropriate.

Sex-specific Z-scores for height and body mass index (BMI) were calculated relative to age using the National Center for Health Statistics 2000 CDC reference data.[17] DXA BMC and aBMD results were converted to sex- and race- (black vs. nonblack) specific Z-scores relative to age based on the published BMDCS reference data.[18] BMDCS normative data for leg lean mass were provided by the study investigator (Zemel, personal communication). DXA Z-scores for TBLH-BMC, spine, total hip, femoral neck, and $1/3^{\text{rd}}$ radius aBMD and leg lean mass were further adjusted for height Z-score according to the method of Zemel *et al.*[19] This method accounts for the age-specific association of DXA Z-scores with stature and provides an unbiased adjustment.

Linear regression models were conducted within the ALL participants after first confirming normative distribution of continuous variables (or log transformation as indicated for non-normative data) in order to examine associations of bone and muscle Z-scores with demographics, disease characteristics (leukemia risk status, age at diagnosis, duration of treatment), medications (cumulative glucocorticoids and antimetabolite chemotherapy), and

interval since completion of therapy. We stratified the DXA data based on time since completion of ALL therapy (early <6 months vs. late ≥ 6 months) at enrollment as it marked the time frame with most notable skeletal changes in our prior report of this cohort.[10] The changes in DXA Z-scores over 12 months after enrollment were examined using a paired t-test. We used multiple linear regression models adjusted for age, sex, race, BMI and enrollment DXA Z-scores to examine the impact of interval since completion of ALL treatment at enrollment on the change in DXA bone outcomes. We used a linear regression model adjusted for enrollment TBLH-BMC and leg lean mass Z-scores to determine whether gains in leg lean mass Z-scores were associated with gains in TBLH-BMC Z-scores after ALL treatment.

We scrutinized correlations between DXA and pQCT bone measures at enrollment and correlations between changes for each parameter over the 12-month study period using Pearson correlation. Lastly, we used a multivariable linear regression model to determine the change in which DXA site best captured the change in tibia pQCT measures of trabecular or cortical vBMD adjusted for change in cortical area following completion of ALL treatment. [10]

3. RESULTS

3.1 Participant and Disease Characteristics

A total of 45 participants completed the enrollment and 12-month visits. The participant and disease characteristics are summarized in Table 1. All but one ALL participant was diagnosed with precursor B-cell ALL and the majority was classified as standard risk, consistent with established ALL demographics. None had central nervous system leukemia or a diagnosis of an endocrine disorder such as amenorrhea or sex hormone deficiency. All participants received glucocorticoids with additional therapy including intravenous methotrexate and oral 6-mercaptopurine exposure, as previously reported.[10]

Height Z-scores were significantly greater at enrollment compared with published values for the BMDCS cohort (0.46 ± 0.94 vs. reference group 0.15 ± 0.82 ; $p < 0.001$).[20] ALL participants demonstrated significantly higher BMI Z-scores at enrollment compared with the BMDCS cohort (0.97 ± 0.83 vs. reference group 0.33 ± 0.82 ; $p < 0.001$). Sex and interval since completion of therapy were not associated with height or BMI Z-scores ($p = \text{NS}$ for both).

3.2 DXA Bone and Lean Mass Outcomes

Table 2 summarizes DXA Z-scores at enrollment and 12 months. At enrollment, TBLH-BMC and 1/3rd radius aBMD Z-scores were not significantly different from the BMDCS reference, spine aBMD was marginally lower ($p = 0.08$), and total hip and femoral neck aBMD were significantly lower, with 11% demonstrating Z-scores <2SD for total hip and femoral neck, respectively.

All DXA bone outcomes increased significantly over the study interval. The gains in Z-scores were less pronounced at the spine. At completion of follow-up, average spine and femoral neck aBMD Z-scores were no longer lower compared with BMDCS. Furthermore,

six (13%) participants demonstrated BMD Z-scores $> +2$ at all measured DXA sites, three (7%) participants at two DXA sites (spine or total hip and distal 1/3 radius aBMD), and three (7%) participants at only one DXA site (TBLH-BMC, spine aBMD or distal 1/3 radius aBMD). In contrast, despite the interval gain, total hip aBMD Z-scores remained lower compared with BMDCS at the follow-up visit. DXA aBMD Z-scores remained < -2 for total hip, femoral neck, or distal 1/3 radius sites in 7 (16%) of ALL participants (all pre-pubertal) at the time of study completion.

The increases in TBLH-BMC Z-scores, and total hip and femoral neck aBMD Z-scores were greater in individuals enrolled within six months of completing ALL therapy, compared with those that enrolled after six months. (Table 3, Figure 2). Similar patterns were observed in the spine and 1/3rd radius though the differences were not significant. Linear regression models examining the change in DXA bone outcomes adjusted for age, sex, race, BMI and DXA Z-scores at enrollment confirmed these findings (data not shown).

Younger age at the time of diagnosis was associated with the greater gains in spine aBMD Z-score [β (95% CI) = -0.15 (-0.27 to -0.04), $p < 0.01$]. This association was not observed at other sites. Leukemia risk group, duration of treatment, or cumulative glucocorticoid or metabolite exposure were not associated with changes in DXA Z-scores, adjusted for enrollment Z-scores and interval since completion of therapy.

Consistent with higher BMI Z-scores, leg lean mass Z-scores were significantly greater in ALL participants compared to BMDCS reference data ($p < 0.001$) at enrollment and follow-up. BMI and leg lean mass Z-scores did not change over the study interval when examined in all ALL participants combined. However, in the stratified analyses summarized in Table 3, both BMI and leg lean mass Z-scores decreased in the early cohort, compared with those enrolled more than six months after completing therapy. The change in TBLH-BMC Z-scores during the study interval was not associated with changes in leg lean mass Z-score over the same interval [β (95% CI) = 0.07 (-0.17 to 0.31), $p = 0.54$], adjusted for results at enrollment. Similar results were seen for DXA aBMD at all sites.

3.3 Correlations between DXA and pQCT Outcomes

The Pearson correlations between tibia pQCT and DXA Z-scores are summarized in Table 4. At the time of enrollment, all DXA outcomes, with the exception of 1/3rd radius aBMD Z-score, were correlated with pQCT cortical area and trabecular vBMD Z-scores ($p < 0.001$). The 1/3rd radius aBMD Z-score demonstrated the strongest correlation with pQCT cortical vBMD Z-score.

As shown in Table 4, changes in DXA bone Z-scores at all sites were positively correlated with changes in tibia cortical area Z-scores. Similarly, gains in TBLH-BMC and total hip and femoral neck aBMD Z-scores were associated with gains in trabecular vBMD Z-score. Distal 1/3rd radius (an entirely cortical site) aBMD Z-scores were not associated with changes in trabecular vBMD Z-score. Of note, gains in spine aBMD Z-scores were not associated with gains in tibia trabecular vBMD Z-score. The finding that changes in cortical vBMD Z-score were negatively associated with changes TBLH-BMC and total hip, femoral neck and 1/3rd radius aBMD Z-scores is consistent with our prior reports that rapid gains in

cortical area are associated with transient decreases in cortical vBMD Z-score.[6, 21] Furthermore, in multivariate regression models, the negative association between DXA-based bone outcomes and cortical density by pQCT no longer remained significant when adjusted for cortical area (Table 5).

3.4 Fracture summary

Nine ALL participants (20%) experienced a total of 10 non-vertebral fractures and two vertebral fractures, as previously reported.[10] The vertebral fractures identified at the time of ALL diagnosis (both in pre-pubertal males) were based on clinical symptoms of back pain, prompting lateral spine imaging by the treating oncologist. Therefore, preexisting or asymptomatic new vertebral fractures were not captured in this study. One patient demonstrated mild (grade 1) at T10 and the other moderate (grade 2) vertebral fracture at T7 location. Seven participants developed fractures during the maintenance phase of ALL therapy and one after completion of treatment (one humerus, three radius/ulna, one tibia/fibula, and two ankle). All fractures occurred with high-impact, physical activity such as running, jumping or playing a sport (e.g. basketball or soccer). Physical activity in ALL was assessed using questionnaires that captured over 30 different sports and play activities categorized as low (e.g. swimming) to high (e.g. gymnastics and basketball) impact activities over the prior year. There was no statistically significant difference in ALL participant physical activity following completion of therapy compared to healthy reference participants (data not shown).

Lastly, there were no differences in DXA outcomes or pubertal status in ALL participants who sustained a fracture compared to participants without fractures. Serum 25OHD levels were not associated with bone Z-scores in ALL participants at either of study visits as previously reported.[10]

4. DISCUSSION

This study is the first longitudinal study to examine changes in DXA measures of bone health at multiple sites in a population of childhood ALL survivors without cranial radiation shortly following completion of therapy. On average, DXA Z-scores at all skeletal sites improved over time, highlighting overall recovery in this population after completion of treatment. However, despite remarkable improvement, total hip Z-scores remained lower compared to reference data. The gains in bone mineral content and density were more pronounced in the cohort shortly after completion of therapy, suggesting the presence of a 'catch up' period during the first 6 months. The increase in lean mass did not appear to explain the increase in DXA bone mineral content or density. When compared to pQCT, the changes in DXA parameters were largely associated with corresponding increases in cortical area.

DXA is the most widely used method to assess bone health in children.[9] The International Society of Clinical Densitometry (ISCD) recommends using the posterior-anterior (PA) spine and TBLH as the preferred anatomical skeletal sites for DXA aBMD and BMC measurements, respectively. In pediatric subjects with chronic diseases that impact bone metabolism, the ISCD considers additional DXA sites such as the proximal femur less

reliable given variability in skeletal development and regions of interest.[9] However, aBMD Z-scores for the proximal femur and total hip correlated well with other skeletal sites during childhood and adolescence in BMDCS,[22] and we showed reliable correspondence between changes in total hip aBMD Z-scores and pQCT measures over the study interval in our cohort of ALL survivors. The ISCD also highlights the insufficiency of a single DXA measurement in dictating initiation of specific therapeutic interventions and emphasizes the importance of fracture history, risk factors and aBMD “trajectory” to provide a complete picture of the disease effects and its therapies.[23]

Conventional and height-adjusted Z-score of DXA PA spine aBMD may not adequately demonstrate increases in trabecular vBMD in children with multiple risk factors for impaired bone accrual. As previously demonstrated by Tsampalieros *et al.*, [6] the comparison of pQCT measures of trabecular vBMD to DXA measures of PA spine aBMD in pediatric patients with Crohn’s disease revealed important differences regarding associations of anthropometry and disease-related factors. These findings highlight the limitations of PA measures of DXA spine aBMD in capturing treatment effects (such as glucocorticoids) on trabecular bone,[6, 24] and suggest that the use of DXA spine aBMD in children with systemic inflammatory or chronic disorders may be inadequate when evaluating treatment effects on the skeleton. Despite glucocorticoid exposure, ALL participants in our study showed no deficits at enrollment in spine aBMD Z-scores (predominant site for trabecular bone) with significant gains of spine aBMD Z-scores within the 12-month study interval compared to reference participants (Table 2). In contrast, concomitant tibia pQCT evaluation demonstrated significant trabecular vBMD Z-score deficits at enrollment in ALL participants independent of age, demographics, and study interval that remained present at the 12-month assessment.[25] These findings may be the result of the concealment of persistent trabecular vBMD deficits by superimposed cortical bone when using the 2-dimensional DXA measurements and further highlights the limitations of DXA PA spine aBMD to assess gains in bone density over time.

The mechanisms underlying enhanced bone mineral density accrual in ALL following completion of therapy remain unclear. At baseline ALL participants demonstrated higher BMI and DXA leg lean mass Z-scores compared with a healthy reference data. These findings are consistent with prior studies in which glucocorticoid-induced obesity is associated with greater height and muscle Z-scores.[26] Over the 12-month study interval from enrollment, the average BMI Z-score decreased but leg lean mass Z-scores remained largely unchanged. Moreover, the gains in bone mineral content and BMD cortical dimensions (i.e. functional muscle bone unit) were not associated with lean mass changes. These findings suggest that enhanced skeletal muscle accrual does not underlie the skeletal improvements in this cohort. However, the extent to which improvements in vincristine-associated neuropathy or glucocorticoid-related muscle dysfunction, physical activity, inflammation, or other osteotoxic exposures (e.g. glucocorticoids) are at play remains undetermined.

Our study has several limitations. First, the absence of bone biopsy data prohibited direct correlations of DXA results with bone microarchitecture, turnover, or mineralization. Second, the DXA and pQCT were not obtained in the same anatomic location. Third, we did

not obtain lateral spine X-rays for the assessment of vertebral fractures. This is an important limitation in light of recent reports of vertebral compression fractures in ALL diagnosis and treatment.[27] While the gains in bone mineral density are overall reassuring and we remain optimistic that ALL survivors demonstrate an improvement in bone health following completion of therapy, given lack of complete skeletal recovery in a sub-group of ALL survivors, future longitudinal studies are beneficial to (1) ensure continued improvement following ALL treatment; (2) identify long-term fracture risk; and (3) assess modifiable factors or other treatments to promote recovery of bone mineral density. Lastly, our results are not generalizable to ALL patients treated with cranial radiation and known pituitary deficits or hypogonadism.

Despite the identified limitations, this study has several notable strengths including longitudinal design to enroll young survivors of childhood ALL without cranial radiation shortly after completion of therapy, and detailed assessment of different anatomical skeletal sites according to the interval since cessation of treatment. Importantly, the use of a large, robust reference with adjustment for height, sex, age, race, and lean mass facilitated evaluation of bone outcomes in the context of the growth and developmental changes that occur in bone density and cortical geometry.

5. CONCLUSION

This longitudinal study highlights the utility of DXA measures at multiple skeletal sites to determine gains in bone mineral content and density in a pediatric cohort shortly after completion of ALL therapy. While TBLH-BMC and spine, femoral neck, and forearm aBMD DXA Z-scores improved over time, the total hip Z-scores, despite recovery, remained lower compared to the reference data. The gains in bone mineral content and density were more pronounced in the cohort shortly after completion of therapy, suggesting the presence of an early ‘catch up’ period. Our findings, along with the availability of robust normative data for proximal femur DXA in pediatric subjects five years of age or greater, suggest a role for including proximal femur measurements in clinical practice and future research.

Acknowledgments

Funding source: The study was supported by NIH grants K07 CA166177 (SMM), K24 DK076808 (MBL), and the CTSA Clinical and Translational Research Center (UL1-RR-024134).

LIST OF ABBREVIATIONS

aBMD	Areal bone mineral density
ALL	Acute lymphoblastic leukemia
BMC	Bone mineral content
BMD	Bone mineral density
BMDCS	Bone Mineral Density in Childhood Study
BMI	Body mass index

CHOP	Children's Hospital of Philadelphia
CV	Coefficient of variation
COG-LTFU	The Children's Oncology Group Long-Term Follow-Up Guidelines
DXA	Dual energy X-ray absorptiometry
ISCD	International Society of Clinical Densitometry
PA	Posterior-anterior
pQCT	Peripheral quantitative computed tomography
SD	Standard deviation
STOPP	Steroid-associated Osteoporosis in Pediatric Population
TBLH	Total body less-head
TBLH-BMC	Total body less-head bone mineral content
vBMD	Volumetric bone mineral density

References

1. Hunger SP, Lu X, Devidas M, Camitta BM, Gaynon PS, Winick NJ, Reaman GH, Carroll WL. Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group. *J Clin Oncol.* 2012; 30(14):1663–9. [PubMed: 22412151]
2. Hogler W, Wehl G, van Staa T, Meister B, Klein-Franke A, Kropshofer G. Incidence of skeletal complications during treatment of childhood acute lymphoblastic leukemia: comparison of fracture risk with the General Practice Research Database. *Pediatr Blood Cancer.* 2007; 48(1):21–7. [PubMed: 16317756]
3. Cummings EA, Ma J, Fernandez CV, Halton J, Alos N, Miettunen PM, Jaremko JL, Ho J, Shenouda N, Matzinger MA, Lentle B, Stephure D, Stein R, Sbrocchi AM, Rodd C, Lang B, Israels S, Grant RM, Couch R, Barr R, Hay J, Rauch F, Siminoski K, Ward LM, Canadian SC. Incident Vertebral Fractures in Children With Leukemia During the Four Years Following Diagnosis. *J Clin Endocrinol Metab.* 2015; 100(9):3408–17. [PubMed: 26171800]
4. Rayar MS, Nayiager T, Webber CE, Barr RD, Athale UH. Predictors of bony morbidity in children with acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2012; 59(1):77–82. [PubMed: 22190454]
5. Lee DC, Campbell PP, Gilsanz V, Wren TA. Contribution of the vertebral posterior elements in anterior-posterior DXA spine scans in young subjects. *J Bone Miner Res.* 2009; 24(8):1398–403. [PubMed: 19257831]
6. Tsampalieros A, Berkenstock MK, Zemel BS, Griffin L, Shults J, Burnham JM, Baldassano RN, Leonard MB. Changes in trabecular bone density in incident pediatric Crohn's disease: a comparison of imaging methods. *Osteoporos Int.* 2014; 25(7):1875–83. [PubMed: 24760243]
7. Leonard MB, Shults J, Zemel BS. DXA estimates of vertebral volumetric bone mineral density in children: potential advantages of paired posteroanterior and lateral scans. *J Clin Densitom.* 2006; 9(3):265–73. [PubMed: 16931343]
8. Wasilewski-Masker K, Kaste SC, Hudson MM, Esiasvili N, Mattano LA, Meacham LR. Bone mineral density deficits in survivors of childhood cancer: long-term follow-up guidelines and review of the literature. *Pediatrics.* 2008; 121(3):e705–13. [PubMed: 18310191]
9. Crabtree NJ, Arabi A, Bachrach LK, Fewtrell M, Fuleihan GEI-Hajj, Kecskemethy HH, Jaworski M, Gordon CM, D. International Society for Clinical. Dual-energy X-ray absorptiometry interpretation

and reporting in children and adolescents: the revised 2013 ISCD Pediatric Official Positions. *J Clin Densitom.* 2014; 17(2):225–42. [PubMed: 24690232]

10. Mostoufi-Moab S, Brodsky J, Isaacoff EJ, Tsampalieros A, Ginsberg JP, Zemel B, Shults J, Leonard MB. Longitudinal assessment of bone density and structure in childhood survivors of acute lymphoblastic leukemia without cranial radiation. *J Clin Endocrinol Metab.* 2012; 97(10): 3584–92. [PubMed: 22865901]
11. Tanner, J., Whitehouse, R., Marshall, W., Healy, M., Goldstein, H. *Assessment of Skeletal Maturity and Prediction of Adult Height (TW3) Method.* WB Saunders; London: 2001.
12. Smith M, Arthur D, Camitta B, Carroll AJ, Crist W, Gaynon P, Gelber R, Heerema N, Korn EL, Link M, Murphy S, Pui CH, Pullen J, Reamon G, Sallan SE, Sather H, Shuster J, Simon R, Trigg M, Tubergen D, Uckun F, Ungerleider R. Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia. *J Clin Oncol.* 1996; 14(1):18–24. [PubMed: 8558195]
13. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res.* 1993; 8(9):1137–48. [PubMed: 8237484]
14. Dam TT, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, Shardell M, Alley DE, Kenny A, Ferrucci L, Guralnik J, Kiel DP, Kritchevsky S, Vassileva MT, Studenski S. An evidence-based comparison of operational criteria for the presence of sarcopenia. *J Gerontol A Biol Sci Med Sci.* 2014; 69(5):584–90. [PubMed: 24737561]
15. Avitabile CM, Leonard MB, Zemel BS, Brodsky JL, Lee D, Dodds K, Hayden-Rush C, Whitehead KK, Goldmuntz E, Paridon SM, Rychik J, Goldberg DJ. Lean mass deficits, vitamin D status and exercise capacity in children and young adults after Fontan palliation, *Heart.* 2014
16. Mostoufi-Moab S, Magland J, Isaacoff EJ, Sun W, Rajapakse CS, Zemel B, Wehrli F, Shekdar K, Baker J, Long J, Leonard MB. Adverse Fat Depots and Marrow Adiposity Are Associated With Skeletal Deficits and Insulin Resistance in Long-Term Survivors of Pediatric Hematopoietic Stem Cell Transplantation. *J Bone Miner Res.* 2015; 30(9):1657–66. [PubMed: 25801428]
17. Ogden CL, Kuczmarski RJ, Flegal KM, Mei Z, Guo S, Wei R, Grummer-Strawn LM, Curtin LR, Roche AF, Johnson CL. Centers for Disease Control and Prevention 2000 growth charts for the United States: improvements to the 1977 National Center for Health Statistics version. *Pediatrics.* 2002; 109(1):45–60. [PubMed: 11773541]
18. Short DF, Gilsanz V, Kalkwarf HJ, Lappe JM, Oberfield S, Shepherd JA, Winer KK, Zemel BS, Hangartner TN. Anthropometric models of bone mineral content and areal bone mineral density based on the bone mineral density in childhood study. *Osteoporos Int.* 2015; 26(3):1099–108. [PubMed: 25311106]
19. Zemel BS, Leonard MB, Kelly A, Lappe JM, Gilsanz V, Oberfield S, Mahboubi S, Shepherd JA, Hangartner TN, Frederick MM, Winer KK, Kalkwarf HJ. Height adjustment in assessing dual energy x-ray absorptiometry measurements of bone mass and density in children. *J Clin Endocrinol Metab.* 2010; 95(3):1265–73. [PubMed: 20103654]
20. Kalkwarf HJ, Zemel BS, Gilsanz V, Lappe JM, Horlick M, Oberfield S, Mahboubi S, Fan B, Frederick MM, Winer K, Shepherd JA. The bone mineral density in childhood study: bone mineral content and density according to age, sex, and race. *J Clin Endocrinol Metab.* 2007; 92(6):2087–99. [PubMed: 17311856]
21. Griffin LM, Thayu M, Baldassano RN, DeBoer MD, Zemel BS, Denburg MR, Denson LA, Shults J, Herskovitz R, Long J, Leonard MB. Improvements in Bone Density and Structure during Anti-TNF-alpha Therapy in Pediatric Crohn's Disease. *J Clin Endocrinol Metab.* 2015; 100(7):2630–9. [PubMed: 25919459]
22. Wren TA, Kalkwarf HJ, Zemel BS, Lappe JM, Oberfield S, Shepherd JA, Winer KK, Gilsanz V, G. Bone Mineral Density in Childhood Study. Longitudinal tracking of dual-energy X-ray absorptiometry bone measures over 6 years in children and adolescents: persistence of low bone mass to maturity. *J Pediatr.* 2014; 164(6):1280–5 e2. [PubMed: 24485819]
23. Bianchi ML, Leonard MB, Bechtold S, Hogler W, Mughal MZ, Schonau E, Sylvester FA, Vogiatzi M, van den Heuvel-Eibrink MM, Ward L, D. International Society for Clinical. Bone health in children and adolescents with chronic diseases that may affect the skeleton: the 2013 ISCD Pediatric Official Positions. *J Clin Densitom.* 2014; 17(2):281–94. [PubMed: 24656723]

24. Leonard MB, Shults J, Long J, Baldassano RN, Brown JK, Hommel K, Zemel BS, Mahboubi S, Whitehead KHoward, Herskovitz R, Lee D, Rausch J, Rubin CT. Effect of Low-Magnitude Mechanical Stimuli on Bone Density and Structure in Pediatric Crohn's Disease: A Randomized Placebo-Controlled Trial. *J Bone Miner Res.* 2016; 31(6):1177–88. [PubMed: 26821779]
25. Mostoufi-Moab S, Ginsberg JP, Bunin N, Zemel B, Shults J, Leonard MB. Bone density and structure in long-term survivors of pediatric allogeneic hematopoietic stem cell transplantation. *J Bone Miner Res.* 2012; 27(4):760–9. [PubMed: 22189761]
26. Foster BJ, Shults J, Zemel BS, Leonard MB. Interactions between growth and body composition in children treated with high-dose chronic glucocorticoids. *Am J Clin Nutr.* 2004; 80(5):1334–41. [PubMed: 15531684]
27. Alos N, Grant RM, Ramsay T, Halton J, Cummings EA, Miettunen PM, Abish S, Atkinson S, Barr R, Cabral DA, Cairney E, Couch R, Dix DB, Fernandez CV, Hay J, Israels S, Laverdiere C, Lentle B, Lewis V, Matzinger M, Rodd C, Shenouda N, Stein R, Stephure D, Taback S, Wilson B, Williams K, Rauch F, Siminoski K, Ward LM. High incidence of vertebral fractures in children with acute lymphoblastic leukemia 12 months after the initiation of therapy. *J Clin Oncol.* 2012; 30(22):2760–7. [PubMed: 22734031]

HIGHLIGHTS

We assessed changes in DXA measures at multiple skeletal sites in children within 2 years of completing ALL therapy.

Changes in DXA outcomes were compared to changes in tibia pQCT trabecular and cortical volumetric BMD and cortical area.

DXA Z-scores at all skeletal sites increased over 12 months, and improvements were more pronounced within 6 months of completing ALL therapy.

Increases in BMC and aBMD Z-scores were not explained by increases in skeletal muscle.

Total hip and femoral neck are useful adjunct measurements to DXA TBLH and spine for assessing gains in aBMD.

Figure 1.

DXA outcomes for total body less-head bone mineral content (TBLH-BMC) (g/cm^2), lumbar spine (g/cm^2), total hip (g/cm^2), and femoral neck (g/cm^2) areal-bone mineral density (aBMD) Z-scores over the 12-month study interval in early (< 6 months) vs. late (≥ 6 months) enrollees from the time of completing ALL therapy. Symbol * denotes statistically significant change over study interval in early vs. late enrollees.

Figure 2.

Panels A-F represent change in DXA outcomes total body less-head (TBLH-BMC) (g/cm^2), total hip (g/cm^2), femoral neck (g/cm^2), and distal 1/3 radius (g/cm^2) aBMD Z-scores compared to tibia pQCT changes in cortical cross-sectional area (mm^2), trabecular vBMD, and cortical density (mg/cm^3) Z-scores according to study interval early (< 6 months) vs. late (> 6 months) from completion of ALL therapy. Symbol X represents early- and hollow circle represents late-interval from completion of ALL treatment, respectively. When compared to pQCT, the changes in DXA parameters in ALL participants were largely associated with corresponding increases in cortical area.

Table 1

ALL Participant and Disease Characteristics

Age, median (range) yr	9.3 (5.1 to 17.8)
Sex, n (% male)	17 (38)
Race, n (% black)	5 (11)
Tanner stage, n (%)	
Pre-pubertal (Tanner 1)	28 (62.2)
Pubertal (Tanner 2-3)	7 (15.6)
Post-pubertal (Tanner 4-5)	10 (22.2)
Age at leukemia diagnosis, median (range) yr	5.9 (1.4 to 15.7)
Duration of therapy, median (range) yr	2.3 (1.3 to 3.4)
Time since completion of therapy, median (range) yr	0.8 (0.0 to 2.2)
Diagnosis, n (%)	
Precursor B ALL	44 (98)
T-cell ALL	1 (2)
Leukemia risk, n (%)	
Standard	30 (67)
High	15 (33)
Cumulative Steroids, n (%), median (range)	
Dexamethasone (g/m ²)	45 (100%) 1.1 g/m ² (0.1 to 1.6)
Prednisone (g/m ²)	13 (29%) 4.7 g/m ² (0.5 to 6.8)
Non-phalangeal fractures, n	(10 fractures; 9 patients)
At Leukemia Diagnosis	2
During Leukemia Treatment	7
Post Leukemia Treatment	1
Laboratory Parameters, median (range)	
Calcium (mg/dL)	9.5 (8.9 to 10.2)
Intact PTH (pg/ml)	27.6 (3 to 66)
25(OH)D (ng/ml)	30.7 (6.9 to 49.3)

Table 2

Anthropometric and DXA Z-scores at enrollment and 12 months in ALL participants

Z-Scores	Baseline ALL vs Reference		12-Month ALL vs Reference		0-12 Month Changes in ALL	
	Median (IQ Range)	P Value	Median (IQ Range)	P Value	Median (IQ Range)	P Value
Anthropometry						
Height	0.46 (−0.20 to 1.14)	<0.001	0.46 (−0.19 to 1.17)	0.01	−0.04 (−0.16 to 0.10)	0.87
BMI	1.07 (0.31 to 1.50)	<0.001	0.93 (0.28 to 1.34)	<0.001	−0.01 (−0.24 to 0.19)	0.31
Bone						
TBLH-BMC	0.18 (−0.41 to 0.69)	0.23	0.41 (−0.30 to 0.85)	<0.01	0.10 (−0.09 to 0.42)	<0.01
LS aBMD	−0.37 (−0.79 to 0.29)	0.08	−0.10 (−0.55 to 0.47)	0.99	0.10 (0.01 to 0.42)	<0.01
Total Hip aBMD	−0.74 (−1.51 to −0.04)	<0.001	−0.55 (−1.05 to 0.18)	0.03	0.39 (−0.10 to 0.69)	<0.001
Femoral Neck aBMD	−0.51 (−1.24 to 0.14)	<0.01	−0.23 (−0.73 to 0.41)	0.46	0.23 (−0.07 to 0.51)	<0.001
Distal 1/3 rd Radius aBMD	−0.20 (−0.81 to 0.51)	0.23	0.04 (−0.76 to 0.74)	0.82	0.28 (−0.10 to 0.69)	<0.01
Muscle						
Leg Lean Mass	0.72 (−0.07 to 1.73)	<0.001	0.76 (0.17 to 1.57)	<0.001	0.05 (−0.28 to 0.40)	0.5

Data presented as median and interquartile (IQ) range. DXA Z-scores are adjusted for height Z-score. IQ=interquartile range

BMI=body mass index; TBLH-BMC=total body less-head bone mineral content; LS =lumbar spine; aBMD=areal bone mineral density

Table 3

Anthropometric and DXA Z-scores and changes in Z-scores from enrollment to 12 months in participants by interval since completion of ALL therapy

	Early * n=17	Late * n=28	P Value
Height			
baseline	0.74 ± 0.81 (0.25 to 1.44)	0.27 ± 0.98 (−0.45 to 0.86)	0.07
follow-up	0.75 ± 0.74 (0.26 to 1.38)	0.26 ± 0.90 (−0.36 to 0.85)	0.05
change	−0.06 ± 0.28 (−0.21 to 0.14)	0.05 ± 0.32 (−0.10 to 0.08)	0.22
BMI			
baseline	1.09 ± 0.85 (0.29 to 1.84)	0.89 ± 0.83 (0.39 to 1.40)	0.43
follow-up	0.84 ± 0.87 (0.24 to 1.70)	0.91 ± 0.81 (0.38 to 1.31)	0.79
change	−0.20 ± 0.42 (−0.39 to 0.06)	0.04 ± 0.25 (−0.17 to 0.25)	0.03
TBLH-BMC			
baseline	−0.15 ± 0.78 (−0.67 to 0.40)	0.35 ± 0.82 (−0.22 to 0.91)	0.04
follow-up	0.40 ± 0.77 (−0.29 to 0.84)	0.36 ± 0.82 (−0.38 to 0.95)	0.87
change	0.44 ± 0.39 (0.22 to 0.80)	0.02 ± 0.30 (−0.11 to 0.21)	<0.001
LS aBMD			
baseline	−0.44 ± 0.62 (−0.85 to −0.12)	−0.07 ± 0.96 (−0.70 to 0.65)	0.11
follow-up	−0.10 ± 0.64 (−0.53 to 0.26)	0.06 ± 0.91 (−0.61 to 0.53)	0.49
change	0.25 ± 0.31 (0.06 to 0.46)	0.11 ± 0.34 (−0.16 to 0.35)	0.19
Total Hip aBMD			
baseline	−1.22 ± 1.32 (−1.96 to −0.51)	−0.44 ± 0.95 (−1.14 to 0.37)	0.03
follow-up	−0.50 ± 1.33 (−1.42 to −0.05)	−0.27 ± 0.94 (−0.98 to 0.56)	0.54
change	0.68 ± 0.49 (0.28 to 0.99)	0.15 ± 0.43 (−0.17 to 0.49)	<0.001
Femoral Neck aBMD			
baseline	−0.94 ± 1.06 (−1.76 to −0.34)	−0.25 ± 1.05 (−0.81 to 0.38)	0.03
follow-up	−0.13 ± 1.20 (−1.01 to 0.57)	−0.11 ± 1.04 (−0.66 to 0.52)	0.97
change	0.67 ± 0.63 (0.21 to 1.19)	0.11 ± 0.39 (−0.13 to 0.31)	<0.01
Distal 1/3rd Radius aBMD			
baseline	−0.03 ± 1.06 (−0.72 to 0.87)	−0.30 ± 1.16 (−1.06 to 0.51)	0.40
follow-up	0.33 ± 0.97 (−0.44 to 0.93)	−0.14 ± 1.18 (−1.03 to 0.70)	0.15
change	0.37 ± 0.46 (0.03 to 0.76)	0.18 ± 0.53 (−0.14 to 0.59)	0.22
Leg Lean Mass			
baseline	1.24 ± 0.99 (0.63 to 1.82)	0.65 ± 1.36 (−0.10 to 1.47)	0.08
follow-up	1.12 ± 0.84 (0.69 to 1.62)	0.83 ± 1.22 (0.01 to 1.23)	0.34
change	−0.24 ± 0.47 (−0.47 to 0.05)	0.21 ± 0.50 (−0.11 to 0.59)	<0.01

* Early refers to participants with enrollment visit < 6 months and late with enrollment visit ≥ 6 months after completion of ALL therapy. Data presented as mean ± SD (interquartile range). DXA Z-scores are adjusted for height Z-score.

BMI=body mass index; TBLH-BMC=total body less-head bone mineral content; LS=lumbar spine; aBMD= areal bone mineral density

Table 4

Correlations (R) among DXA and Tibia pQCT Z-scores in ALL participants at baseline and change over the 12-month study interval.

DXA Z-scores	Tibia pQCT Z-scores					
	Baseline Correlation * P value			Change Correlation * P value		
	Cortical Density	Cortical Area	Trabecular vBMD	Cortical Density	Cortical Area	Trabecular vBMD
TBLH BMC	0.33 0.02	0.72 <0.001	0.71 <0.001	-0.35 0.02	0.67 <0.001	0.40 <0.01
LS aBMD	0.30 0.04	0.47 <0.001	0.47 <0.001	-0.24 0.12	0.42 <0.01	0.21 0.17
Total Hip aBMD	0.05 0.74	0.54 <0.001	0.62 <0.001	-0.37 0.01	0.60 <0.001	0.37 0.01
Femoral Neck aBMD	0.25 0.09	0.60 <0.001	0.71 <0.001	-0.29 0.05	0.56 <0.001	0.37 0.01
Distal 1/3 Radius aBMD	0.48 <0.001	0.24 0.10	0.25 0.09	-0.31 0.04	0.37 0.01	0.23 0.14

DXA Z-scores are adjusted for height Z-score; pQCT Z-scores are adjusted for tibia length Z-score

* Pearson correlation (R); Change = (follow up – baseline)

pQCT=peripheral quantitative computed tomography; vBMD=volumetric bone mineral density TBLH-BMC=total body less-head bone mineral content; LS=lumbar spine; aBMD=areal bone mineral density

Table 5

Changes in DXA Z-score outcomes relative to changes in tibia peripheral QCT Z-scores

Change DXA Z-score	Change pQCT Z-score β (95% CI); P value	
	Cortical Density	Cortical Density adjusted for Cortical Area
TBLH-BMC	-0.19 (-0.31 to -0.07) < 0.01	-0.01 (-0.19 to 0.18) 0.71
Spine aBMD	-0.06 (-0.17 to 0.04) 0.26	0.15 (-0.0 to 0.31) 0.44
Total hip aBMD	-0.25 (-0.41 to -0.09) < 0.01	-0.03 (-0.23 to 0.17) 0.41
Femoral neck aBMD	-0.25 (-0.42 to -0.07) < 0.01	-0.08 (-0.31 to 0.14) 0.31
Distal 1/3 Radius aBMD	-0.17 (-0.32 to -0.02) 0.03	-0.09 (-0.28 to 0.10) 0.35

CI= Confidence Interval; TBLH=Total Body Less-Head; BMC= Bone Mineral Content; aBMD=areal Bone Mineral Density