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Bone Mineral Density after Bone Marrow Transplantation in Childhood: Measurement and Associations

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This study examined the bone mineral density (BMD) of 46 (median age 16.3, 8-29) survivors of autologous and allogeneic bone marrow transplantation (BMT). Areal (g/m2) BMD was acquired with dual energy x-ray absorptiometry and volumetric (g/cm3) BMD values were calculated. Abnormal BMD was identified in 24% (11/46) of survivors with areal measures and 22% (10/46) with volumetric measures. Comparison of areal and volumetric BMD revealed the measures were highly correlated ($r = 0.73$, $p<0.001$) but clinical diagnosis of osteopenia/osteoporosis were not consistent. Volumetric z-scores were higher for 7/8 of the survivors who were < 3rd percentile for height. Associations of BMD and body composition and disease and treatment factors were assessed with multiple linear regression. When controlling for other significant associations and cumulative steroid dose, the body composition measure of fat mass index (FMI) was associated with higher volumetric BMD z-scores (CI: 0.006, 0.193; $p = 0.037$). CNS irradiation (CI: -1.710,-0.200; $p = 0.015$), age at time of testing (CI: -0.116, -0.024; $p = 0.004$) and female sex (CI: -1.375, -0.155; $p = 0.015$) were associated with lower volumetric BMD z-scores. Conclusions: Childhood BMT survivors are at risk for diminished BMD. Areal and volumetric DEXA derived measures of BMD are highly correlated and volumetric measures may correct for underestimation of BMD in BMT survivors who are small for age. Survivors who received CNS irradiation, are older and female may be at greater risk for diminished BMD while fat mass is associated with higher BMD in childhood BMT survivors.

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INTRODUCTION

Diminished bone mineral density (BMD) is a known complication after bone marrow transplantation (BMT) in children [1-3]. Endocrine dysfunction, irradiation, corticosteroids, and chronic graft versus host disease (cGVHD) have been identified as risk factors for diminished BMD in childhood cancer survivors [4-9]. Our understanding of the mechanisms and risks for diminished BMD after childhood BMT remains incomplete, however.

Measurement of BMD density in childhood cancer survivors has proved problematic. In children, the World Health Organization (WHO) criteria are used for the clinical diagnosis of osteopenia/osteoporosis based on *z*-scores calculated from age-, sex-, and race-matched reference data. Many childhood BMT survivors are small for their age, making the standard *z*-score comparisons based on age and sex alone inaccurate, leading to systematic underestimation of BMD in smaller children [10]. Current recommendations call for the use of 3-dimensional (volumetric) measurements of BMD in this population [11].

Dual-energy x-ray absorptiometry (DEXA) is the most frequently used technique to assess BMD. DEXA is readily available and associated with very low exposure to ionizing radiation. It acquires BMD measurements in 2 dimensions, with calculations required to obtain volumetric measurements [12]. We were unable to identify any previous studies comparing areal and calculated volumetric BMD measurements from DEXA scans in childhood BMT survivors.

Maintenance of appropriate BMD is multifactorial, influenced by other components of body composition, fat mass, and fat-free mass. The associations between BMD and fat mass and fat-free mass vary according to the population studied, but might explain up to 31% of the variance in BMD seen in healthy

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populations [13]. We identified no previous studies examining the associations between BMD and body composition in childhood BMT survivors. Knowledge of these associations might be important to improving our understanding of BMD outcomes and possibly guiding treatment decisions.

The aims of the present study were to evaluate the lumbar spine BMD of BMT survivors, compare the DEXA scan acquired areal and volumetric measurements of BMD, explore the relationship between BMD measurements and body composition, and identify disease and treatment factors that predict diminished BMD.

SUBJECTS AND METHODS

Subjects

Childhood BMT survivors who were at least 2 years posttransplantation were recruited from an established survivor clinic, and recruitment letters were mailed to those whose names and addresses were generated from the institutional BMT database. Twelve survivors were recruited from 160 mailings; the remaining 34 were recruited from clinic visits. This protocol was approved by the Johns Hopkins Institutional Review Board, and informed consent was obtained for all participants. Parental consent and subject assent was obtained for those under the age of 18 years.

Variables Analyzed

A medical records review was used to gather data on age at time of BMT, years since BMT, autologous versus allogeneic BMT, preparative regimen including total body irradiation (TBI) or central nervous system (CNS) irradiation (not just TBI), and history of cGVHD. In addition, medical records were reviewed to determine prednisone equivalent cumulative steroid dose, including pretransplantation regimens until resolution of cGVHD. Patient/family reports and medical record reviews were used to assess endocrine function, which was categorized as 1 (normal, no endocrinopathies or thyroid-stimulating hormone suppression therapy only) or 2 (abnormal, growth hormone and/or gonadal hormone replacement). Physical examination determined pubertal development by Tanner stage (pubic hair). Height was measured to the nearest centimeter with a stadiometer. Kilograms of fat-free mass and fat mass were obtained from DEXA data and were converted to fat mass index (FMI) and fat-free mass index (FFMI) values using the following formula: weight (kg)/height (m^2).

BMD Measurement

BMD of the lumbar spine (L1-L4) was determined by DEXA (Prodigy; GE Healthcare, Buckinghamshire, UK), which provided areal BMD (g/cm^2) and age/sex/ethnic matched z-scores derived from U.S. Food and Drug Administration approved healthy controls. Volumetric BMD (g/cm^3) values for L1-L4 were calculated to determine the apparent BMD using the formula: volumetric BMD = BMD $(4/(\pi \times \text{width}))$ [14]. Volumetric BMD z-scores were calculated from published lumbar spine volumetric BMD (g/cm^3) reference data on 444 age- and sex-matched healthy controls obtained using the same DEXA equipment and calculated with the foregoing formula [15]. The z-scores from each measurement were used to identify survivors meeting WHO criteria for osteopenia (z = -1 to -2.5) and osteoporosis (z <-2.5) [16].

Data Analysis

Stata 10 (StataCorp, College Station, TX) was used for all analyses. The z-scores for areal (g/cm^2) and volumetric (g/cm^3) BMD measurements were calculated as described earlier and compared with WHO criteria for osteopenia and osteoporosis. Pearson's correlation was used to examine the relationships between areal and volumetric BMD measurements.

Univariate and multivariate analysis for volumetric z-scores and predictor variables were performed. Multivariate model selection was performed with forward selection. Covariates considered for the regression model included age, age at time of BMT, years after BMT, Tanner stage, endocrine function, CNS irradiation, TBI, type of BMT, cGVHD, cumulative steroid dose, FMI, and FFMI [4-6]. Significance was set at $\alpha = .05$.

RESULTS

Subjects

Characteristics of the study subjects are summarized in Table 1. The distribution of indications for transplantation and transplant types were reasonably representative of the distributions at the pediatric BMT program at Johns Hopkins. In addition, approximately 25% of the BMTs performed at Johns Hopkins are done for nonmalignant diseases. In this study, only 8 survivors had a nonmalignant condition, including aplastic anemia and X-linked autoimmune/allergic dysregulation syndrome, but no survivor had thalassemia. Three of the survivors who received CNS irradiation for a hematologic malignancy also had a preparative regimen including TBI. Tanner stages were bimodal and appropriately reflective of age.

BMD Measurement

BMD outcomes for BMT survivors were analyzed using z-scores for areal and volumetric measures. Using areal lumbar BMD z-scores, 22% (10/46) of the survivors met the criteria for osteopenia, and 2%

Table 1. Subject Characteristics (n = 46)

Age at time of testing, years, median (range)	16.3 (8-29)
Age at BMT, years, median (range)	8 (0-21)
Years since BMT, median (range)	8 (2-22)
Males, n (%)	
Tanner stage, n (%)	27 (57%)
I	14 (30%)
II	4 (8%)
III	1 (2%)
IV	4 (8%)
V	25 (54%)
Allogeneic BMT, n (%)	30 (65%)
TBI-based preparative regimen, n (%)	15 (33%)
CNS irradiation, n (%)	8 (17%)
History of cGVHD, n (%)	8 (17%)
Abnormal endocrine function, n (%)	15 (30%)
Cumulative steroid dose, mg/m^2	533 (0-68,517)
Fat-free mass index, kg/m^2, mean ± SD	13.8 ± 2.2
Fat mass index, kg/m^2, mean ± SD	6.0 ± 3.3

BMT indicates bone marrow transplantation; TBI, total body irradiation; cGVHD, chronic graft-versus-host disease. Subjects were recruited over an 18-month period from an established survivor program with approximately 630 participants, of whom approximately 200 have undergone BMT.

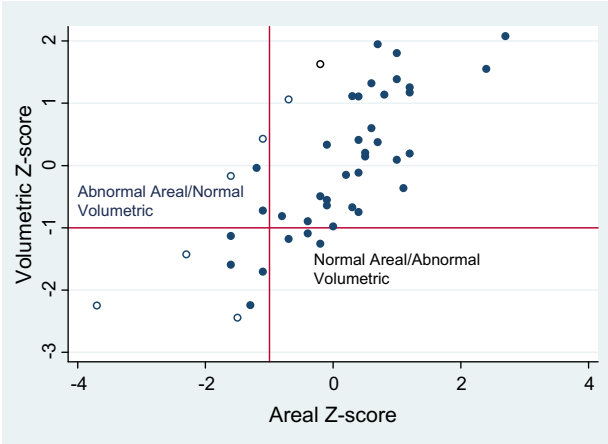

Figure 1. Correlation of areal and volumetric lumbar spine BMD z-scores. The open circles indicate subjects under the 3rd percentile for height according to CDC growth charts.

(1/46) did so for osteoporosis. Using volumetric lumbar spine BMD *z*-scores, 22% of the survivors (10/46) met the criteria for osteopenia, and none met the criteria for osteoporosis. Characteristics of survivors with diminished volumetric BMD are presented in Table 3.

The comparison of areal and volumetric measures included an analysis of values for survivors who were small for their age and differences in WHO diagnoses for the 2 measurements. As expected, areal lumbar and volumetric lumbar BMD *z*-scores were correlated (r = 0.73; P <.001). For the 8 survivors who were below the 3rd percentile for height (according to Centers for Disease Control and Prevention [CDC] growth charts), 7 had higher *z*-scores with the volumetric measurements. The only survivor who met the criteria for osteoporosis had an areal *z*-score of -3.7 and a volumetric *z*-score of -2.25. This survivor was an 18-year-old male with a height of 153 cm (well below the 3rd percentile).

Differences in classification of osteopenia/osteoporosis between the 2 measurements were identified (Figure 1). Four of the 11 (36%) survivors with osteopenia identified using areal measurements had a normal volumetric *z*-score, and this group had a median height *z*-score of -1.37 (INTERQUARTILE RANGE 1.27), calculated from National Health and Nutrition Examination Survey (NHANES) data [18]. Three of the 10 (30%) survivors with osteopenia identified using volumetric measurements had a normal areal *z*-score, and the median height *z*-score for this group was 0.39 (iqr 1.5).

Regression Analysis

As supported by our data, volumetric measurement is the recommended method for evaluating BMD in childhood cancer survivors, and thus is the method used for the predictive models. On univariate analysis, only age (95% confidence interval [CI], -0.127 to 0.022; P = .007) and CNS irradiation (95% CI, -1.870 to -0.089; P = .032) had statistically significant associations with volumetric *z*-scores. Multiple linear regression was performed with volumetric *z*-scores as the response variable (Table 2). Controlling for cumulative steroid dose, CNS irradiation, female sex, and older age at the time of testing were significantly associated with lower volumetric *z*-scores. FMI was positively associated with volumetric *z*-scores.

DISCUSSION

This study has identified several novel findings relevant to the detection of and risk factors for diminished BMD in survivors of BMT during childhood. First, volumetric measurement appears to be the most appropriate way to evaluate survivors who are small for their age. Second, CNS irradiation, older age at time of testing, and female sex are risk factors for diminished BMD. Third, we found a positive association between FMI and BMD that has not been described in previous studies of childhood BMT survivors.

BMD Measurement

The appropriate measurement of BMD in BMT survivors is an important topic that remains under debate. Although the use of volumetric measurement of BMD has been recommended, the most suitable examination technique has not yet been identified. The most frequently used radiologic techniques for measuring volumetric BMD are quantitative computed tomography (QCT) and DEXA. Although QCT provides a direct measurement of volumetric BMD, it is associated with higher doses of ionizing

Table 2. Characteristics of Survivors with Diminished Volumetric BMD

Diagnosis	BMD z-Score (Volumetric)	Sex	Age at Testing, Years	Years Out	cGVHD	Endocrine Dysfunction	Cumulative Steroid Dose, mg/m^2
Neuroblastoma	−1.26	Female	9	5	−	−	0
CNS tumor	−2.25	Male	19	7	−	+	181
ALL	−2.25	Female	27	16	+	+	10,183
CNS tumor	−1.71	Male	10	2	−	+	183
ALL	−1.59	Female	20	2	+	−	5139
Rhabdomyocarcoma	−1.43	Male	19	17	−	+	24
Wilms' tumor	−1.26	Female	23	5	−	+	0
AML	−1.18	Female	25	19	−	−	6740
Aplastic anemia	−1.13	Female	13	4	−	−	0
AML	−1.10	Male	26	4	−	−	0

BMD indicates bone mineral density; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia.

radiation and thus is used less frequently than DEXA. Although DEXA is considered the gold standard for measuring BMD with minimal ionizing radiation, it requires manual calculation [10]. Identifying the safest and most accurate approach to measuring BMD after BMT is important to both clinical practice and future research.

In this study, the prevalence of diminished BMD (osteopenia/osteoporosis) was similar regardless of whether areal or volumetric measurement was used (areal, 11 of 46 subjects; volumetric, 10 of 46 subjects). Although the areal and volumetric lumbar spine BMD measurements were significantly correlated, as expected, there were important differences in the classification of diminished BMD in individual survivors. These incongruent findings are significant for individual survivors because the monitoring of, and interventions for, diminished BMD are based on z-score findings. Using thresholds defined by the WHO for osteopenia/osteoporosis, 30% of the subjects with osteopenia identified by volumetric z-score had a normal areal z-score and were of average height. Conversely, 36% of the subjects with osteopenia identified by areal z-score had a normal volumetric z-score; these survivors were small for their age, and their higher volumetric scores likely reflects correction of an underestimated areal measurement. We found that 88% of survivors who were below the 3rd percentile for height had higher BMD z-scores with volumetric measurement, providing further evidence that DEXA-derived volumetric measures may correct for underestimation of BMD in this population.

Table 3. Factors Associated with Volumetric BMD in Multivariate Analysis

Covariate	Coefficient*	95% CI	*P* Value
Female	−0.765	−1.375 to −0.155	.015
Age	−0.070	−0.116 to −0.024	.004
CNS irradiation	−0.954	−1.710 to −0.200	.015
FMI (kg/m^2)	0.099	0.006 to 0.193	.037
$R^2 = 0.345$			

BMD indicates bone mineral density; FMI, fat mass index; FFMI, fat-free mass index.

*Multiple linear regression was performed using volumetric BMD z-score as the response variable and considering the following covariates: age, sex, Tanner stage, age at BMT, years since BMT, type of BMT, TBI based preparative regimen, CNS irradiation, history of cGVHD, abnormal endocrine function, FFMI, FMI, and controlling for cumulative steroid dose. Forward selection with $\alpha = 0.1$ was used to determine the final model, and $\alpha = 0.05$ was used for significance.

Our findings suggest that DEXA-derived volumetric calculation of lumbar BMD is the most appropriate method for BMT survivors who are small for their age. Although the most appropriate measure to use in diagnosis and subsequent treatment of osteopenia/osteoporosis in survivors who are not small for their age is not determined by the results of this study, we recommend standardizing a volumetric measurement for all childhood BMT survivors.

BMD Associations

In addition to measurement issues, the understanding of mechanisms necessary to develop and maintain optimal BMD in cancer survivors is evolving. The importance of understanding the full spectrum of factors that contribute to BMD is critical in evaluating causes and developing interventions for diminished BMD in BMT survivors. Body composition (fat mass and fat-free mass) is associated with BMD in healthy populations, but an evaluation of these associations in childhood BMT survivors has not yet been reported [13].

In this study, we found that FMI was associated with higher volumetric z-scores. Fat mass has been associated with increased BMD in obese children and adolescents and is thought to result from the increased mechanical loading placed on the bones [17]. Another possible explanation is elevated leptin levels associated with obesity. Leptin stimulates chondrocytes and is hypothesized to contribute to BMD in obese individuals [17,18].

The positive effects of fat mass on BMD are accompanied by health risks associated with obesity, such as diabetes and heart disease. Therefore, it would be inappropriate to suggest increasing fat mass beyond healthy recommendations in survivors when other means of maintaining and increasing BMD exist. Studies in

other populations have shown that exercise training that increases lean mass and fitness can maintain or increase BMD, despite the fact that exercise also decreases body fat [19]. Our findings suggest that exercise interventions designed to increase BMD in childhood BMT survivors should recognize the important relationships among bone, muscle, and fat and capitalize on interventions that will have a positive impact on overall health.

Our analysis identified other treatment and demographic associations as well. Our findings confirm previous studies that found an association between CNS irradiation and decreased BMD [8,20,21]. There are several explanations for this finding. In 75% of the survivors who received CNS irradiation, the lumbar spine was included in the field; thus, a radiation-induced drop in chondrocytes might have contributed to the association with lower lumbar BMD [22]. The doses and sites of CNS irradiation varied, and the sample was too small to allow examination of site and dose associations, but this would be important to consider in future studies.

In other CNS-irradiated patient populations, antiepileptic agents and physical disability have been associated with diminished BMD [23], which also might help explain the relationship identified in the present study. Although no survivor in our study was currently receiving an antiepileptic agent, some might have had previous exposure to these agents. Finally, 2 of our survivors who received CNS irradiation were treated for CNS tumors, which require higher doses of radiation in addition to surgical interventions. Both of these survivors had significant ataxia that limited their physical activity, especially high-impact activities, which are known to be important for improving and maintaining BMD.

In addition, CNS irradiation may be associated with pituitary dysfunction, resulting in thyroid, gonadal, and/or growth hormone deficiency, all of which can negatively affect BMD. Even though all of the survivors with diagnosed hormone deficiency were receiving hormone replacement therapy, there might have been more subtle, untreated abnormalities in the CNS-irradiated group. For example, subnormal androgen levels have been identified in female BMT survivors, and testosterone replacement has been shown to improve BMD in women with hypogonadal functioning because of hypopituitarism [24]. In the present study, endocrine function and replacement data were based solely on medical record review and subject reports; levels were not measured. Future studies should consider further evaluation of endocrine function and the impact of current hormone replacement strategies on BMD.

We also found that older age at the time of testing was associated with lower volumetric z-scores. The lower volumetric z-scores in older survivors emphasizes the need for screening and intervention in childhood survivors to achieve and maintain optimal peak bone mass.

Female BMT survivors were found to have lower volumetric z-scores. In healthy older females, osteoporosis and osteopenia are major health concerns; compromised BMD after BMT will make this an even greater concern for female survivors. Diminished BMD in female childhood BMT survivors has previously been reported and attributed to gonadal dysfunction [1]. As noted earlier, endocrine abnormalities not readily diagnosed in female survivors, including androgen deficiency, might contribute to the negative association between female sex and volumetric BMD found in our study. Six of the 8 (75%) females with abnormal endocrine function were receiving gonadal hormone replacement therapy at the time of testing. Research is needed to identify the optimal hormone replace strategies in female BMT survivors.

Steroid treatment has been implicated in diminished BMD before and after childhood BMT [7,25]. However, we found that cumulative steroid dose, including therapies before BMT through the resolution of cGVHD, was not associated with lower volumetric z-scores in either univariate analysis ($\beta = 0.000$; $P = .150$) or multivariate analysis ($\beta = 0.000$; $P = .073$). A possible explanation for this finding includes the fact that the previous studies were conducted in childhood BMT survivors closer to the time of treatment (up to 12 months post-BMT) [7]. Evidence exists suggesting that the effects of steroids on BMD are reversible, and that BMD increases after discontinuation of steroid therapy [26]. In our study, the mean time post-BMT was 8 years (range, 2-22 years), and no subject was actively taking steroids. Our findings suggest that the diminished BMD associated with steroid treatment is time-limited and might recover over time in childhood BMT survivors.

Therapeutic Considerations

Treatment of diminished BMD after childhood cancer has not been well studied. Most studies have had small sample sizes, included only hematologic malignancies, and used bisphosphonates [27-30]. Biphosphonate therapy also has been used in the treatment and prevention of diminished BMD in adults undergoing BMT [31-33]. Although these previous studies have shown that bisphosphonates are well tolerated and improve BMD in these populations, more information is needed on which to base treatment recommendations. Certainly treatment of any underlying condition, such as an endocrinopathy, is recommended in survivors with diminished BMD. Treatment with calcium, vitamin D, and exercise has been studied in healthy pediatric populations and has shown varying degrees of effectiveness [33-36]. An

ongoing, longitudinal study of these interventions in childhood ALL survivors might validate the effectiveness of such a treatment approach in this population [37].

In conclusion, maintenance of appropriate BMD is multifactorial, and the etiology of diminished BMD may change over time in childhood BMT survivors. Our findings confirm that childhood BMT survivors are at risk for abnormal BMD, primarily osteopenia. Osteopenia in younger populations has been shown to predict future osteoporosis and fractures [38]. Early detection of diminished BMD will allow for appropriate interventions and may prevent future disability.

We recommend the use of volumetric measurements of BMD in survivors who are small for their age. Further research comparing other methods, including QCT, is needed to confirm that DEXA-derived volumetric measures are most appropriate for all BMT survivors.

The FMI value was found to have a positive association with BMD. Interventions that increase fat-free mass and improve overall fitness may help maintain BMD in survivors who are obese. The significance of fat mass is an important addition to the understanding of BMD outcomes in BMT survivors and may help guide interventions in individual patients. Additional risk factors for diminished BMD identified in this study include treatment with CNS irradiation and female sex. Further research is needed to elucidate the underlying mechanisms for these associations, and these studies should include the evaluation of possible endocrine etiologies and interventions.

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