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Association of Muscle Strength and Bone Mineral Density in Adult Survivors of Childhood Acute Lymphoblastic Leukemia

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Abstract

Objectives—To investigate the association between bone mineral density (BMD) and muscle strength in survivors of childhood acute lymphoblastic leukemia (ALL), a population at increased risk for both decreased BMD and muscle strength from cancer and its treatment.

Design—Cohort data from the St Jude Lifetime Cohort (SJLIFE) study.

Setting—Department of Cancer Control at St Jude Children's Research Hospital.

Participants—Subjects were adults enrolled in St Jude Lifetime Cohort study and treated for childhood ALL between 1962 and 1999. As part of a comprehensive evaluation, participants had dual energy x-ray absorptiometry (DEXA) scans and muscle strength testing. The participants consisted of 261 women and 232 men who were 20.4 to 49.8 years old (median, 35.7y), and 12.7 to 46.5 years from diagnosis of childhood ALL (median, 27.2y).

Interventions—Not applicable.

Main Outcome Measures—BMD was determined by DEXA scan. Muscle strength of upper and lower extremities was assessed with physical performance testing.

Results—After adjusting for covariates, we found significant ($P < 0.005$) associations between BMD and muscle strength in lower extremities (R^2 range, 0.33–0.40) and strong, significant associations in upper extremities (left-side $R^2 = 0.558$; right-side $R^2 = 0.560$).

Conclusions—Muscle strength was associated with BMD in the extremities of long-term survivors of childhood ALL, a finding suggesting that muscle strengthening interventions may improve bone health in them.

Keywords

Bone density; Muscle strength; Rehabilitation

Treatment for pediatric acute lymphoblastic leukemia (ALL) has improved such that 85% of children with ALL will survive into adulthood.¹ Unfortunately, ALL and its treatment predispose these survivors to an increased risk of developing health problems when compared to their siblings or the general population.²⁻⁴ ALL survivors are at particular risk for loss of lean muscle mass and strength, as well as low bone mineral density (BMD).^{2,3,5-8}

At the time of diagnosis, children with ALL may have bony infiltration by disease, accompanied by reduced serum levels of bone formation biomarkers, resulting in decreased BMD.⁵ BMD is further compromised by exposure to osteotoxic chemotherapy including glucocorticoids, methotrexate, and alkylating agents.^{5,9-13} Fragility fractures and osteonecrosis may develop during treatment² and subsequent periods of immobilization may further contribute to bone loss. Suboptimal nutritional intake, treatment-related fatigue, loss of lean mass, intramuscular fat deposition, and associated decrements in muscular strength may also contribute to reduced BMD.¹⁴⁻¹⁶ Dynamic mechanical forces, applied by muscle on bone, influence skeletal morphology.¹⁷ The time-dependent transduction of force from attached muscle generates a mechanical strain as collagen is formed.¹⁸⁻²⁰ Increases in mechanical strain (eg, physical activity) result in bone deposition; decreases in mechanical strain (immobility or disability) result in bone resorption.²¹ Because ALL usually occurs during periods of rapid physical development and growth, these children may never reach their physical and muscular potential.²² BMD among adult survivors of ALL is estimated to be present in 20% of survivors, compared to an expected 5% of the average population.⁸ Specific testing of muscular strength in a subgroup of young adult survivors of childhood ALL indicates that muscular weakness is also a significant issue for 25% to 30% of leukemia survivors.⁷

Little research has been reported on the association between muscle strength and BMD in adult survivors of ALL. If a relationship exists, it will provide insight into a potential intervention to improve bone health. Resistance exercise has been shown to improve muscular strength and bone health in persons with chronic disease,²³⁻²⁵ and such interventions may improve strength and BMD in young ALL survivors. Thus, we examined the association between muscle strength and BMD among a large group of survivors of childhood ALL.

METHODS

Study Participants

Study participants were enrolled in the St Jude Lifetime Cohort (SJLIFE), a study designed to evaluate medical and psychosocial late effects of childhood cancer and its treatment.²⁶ Potentially eligible participants were treated at St Jude Children's Research Hospital for childhood cancer between 1962 and 1999. All participants were 18 years of age or older at enrollment into SJLIFE and had survived at least 10 years since their original cancer diagnosis. Protocol enrollment started in November of 2007 and is ongoing. Participants eligible for these analyses included survivors of childhood ALL who participated in medical follow-up and functional assessments by April 30, 2010. All study documents were approved by the St Jude Children's Research Hospital Institutional Review Board. Written informed consent was obtained from each study participant. Data were managed according to the Health Insurance Portability and Accountability Act of 1996.

Among the first 1122 ALL survivors eligible to participate, 941 (84%) were contacted and 739 (79% of contacted) agreed to return to St Jude for a comprehensive medical evaluation. The remainder agreed to provide self-reported outcomes through completion of study questionnaires (fig 1); a small proportion of these also agreed to undergo a limited local evaluation, including assessment of vital signs, body mass index, and blood collection for

laboratory studies. As of April 30, 2010, 527 ALL survivors had completed their medical evaluation. Among these 527 participants, 12 (2%) were unable to complete the physical performance portion of the assessment, and 22 (4%) did not have a BMD assessment. Of these 22, 14 patients exceeded the weight limit of the examination table, and 8 declined to have the exam. Analyses focus on the 493 survivors who completed both the physical performance and BMD assessment.

Dual Energy X-ray Absorptiometry

The primary outcome of interest for this analysis was whole arm and whole leg BMD (g/cm³) obtained by dual energy x-ray absorptiometry (DEXA). Whole body, anterior, lateral lumbar DEXA were performed using a Hologic 4500 QDR-A fan beam system.^a All acquired BMD values were generated using the QDR software for Windows, version 12.1. BMD and lean body mass by anatomic sites were abstracted from DEXA-determined values. BMD determined in our cohort was compared with the normative database provided by the manufacturer.

Muscle Strength

Handgrip strength in kilograms was measured using a Jamar hand-held dynamometer.^b Participants were seated with the shoulder at 0° to 10° and the elbow at 90° of flexion.²⁷ The forearm was positioned neutrally. Each participant completed 3 trials, and the averages were analyzed. Lower-extremity strength values were evaluated on the Biodex III isokinetic dynamometer.^c Participants were seated and secured on a padded seat with manufacturer-provided positioning straps at the chest, waist, and thigh. The anatomical axis of the joint was aligned with the mechanical axis of the dynamometer. Average peak torques (Nm) were recorded during 5, 10, and 15 isokinetic contractions of the quadriceps at 90°, 180°, and 300° per second, respectively, and during 5 and 10 isokinetic contractions of the plantar and dorsiflexors at 60° and 90° per second, respectively. Calibration was performed before each session according to the manufacturer's instructions. Subjects warmed up by walking for 5 minutes prior to testing.

Additional Independent Variables

Demographic and treatment variables were abstracted from medical records as part of the SJLIFE Study²⁶ and included relevant disease-related information, such as age at diagnosis of ALL, time since diagnosis, height, weight, use of osteoporosis medication, age at examination, chemotherapy received (including cumulative doses for 22 specific agents), surgical procedures, and radiation treatment fields, dose, and energy source. Because oral glucocorticoid therapies are completed by patients at home during treatment for leukemia, the scheduled dose by protocol was used to study the potential effect of glucocorticoids on BMD. Circulating total insulin-like growth factor 1 (IGF-1) level was quantified because this key growth factor is directly reduced by glucocorticoids and in individuals who have been treated with cranial radiation, often leading to growth inhibition and decreased bone mineralization.^{12,13,28} Fasting serum IGF-1 levels were measured with a chemiluminescence immunoassay on the Siemens Immulite 2000 immunoassay analyzer.^d

^aHologic Inc, 35 Crosby Dr, Bedford, MA 01730.

^bPatterson Medical/Sammons Preston, 1000 Remington Blvd, Ste 210, Bolingbrook, IL 60440-5117.

^cBiodex Medical Systems, 20 Ramsay Rd, Shirley, NY 11967-4704.

^dSiemens HealthCare Diagnostics, 1717 Deerfield Rd, Deerfield, IL 60015.

Statistical Analysis

Descriptive statistics were generated for all demographic and clinical variables. Data distributions were examined for normality prior to conducting statistical analyses. Pearson correlation coefficients were used to evaluate crude associations between lean body mass and muscle strength, and between muscle strength and corresponding limb BMD.

After crude analyses, potential confounders of the association between muscle strength and bone density were evaluated using multiple variable linear regression. Those covariates that did not appreciably change the parameter estimate of the primary predictor (muscle strength) were not included in the final models.²⁹ Potential covariates included sex, race, age at examination, age at diagnosis, time since diagnosis, a history of limb surgery, IGF-I level, cranial radiation, and treatment-related doses of glucocorticoid, methotrexate, and cyclophosphamide. The final models examining the association between muscle strength and corresponding limb BMD included the following covariates: age at diagnosis, sex, time since diagnosis, height, weight, osteoporosis medication use, cranial radiation, and treatment-related glucocorticoid dose. All data were analyzed with SAS version 9.1.3.^e

RESULTS

Participant Characteristics

Participant characteristics are shown in table 1. The subjects included 232 men (47%) and 261 women (53%) with a median height of 166.3cm (range, 138.5–194.0cm) and a median weight of 81.1kg (range, 37.3–132.1kg). The median age at diagnosis of ALL was 5.0 years (range, 0.2–18.8y), and participants had a median age of 32.6 years (range, 20.4–54.4y) at time of examination. The median time since diagnosis was 27.2 years (range, 12.7–46.5y). The median treatment-related glucocorticoid dose was 7610mg/m² (range, 1120–23,632mg/m²). Only 3% of participants reported taking osteoporosis medications in the 3 months preceding their examinations, and 70% of participants were treated with cranial irradiation (median dose, 1800cGy; range, 0–4670cGy). Mean height *z* scores were decreased in this population (-0.6 ± 1.2) as were mean BMD lumbar *z* scores (-0.3 ± 1.2). BMD *z* scores less than -2.5 were prevalent among 3% and *z* scores between -1.0 and -2.5 were prevalent among 26% of survivors. There were strong correlations between upper- and lower-extremity BMD (0.74, $P < 0.001$), and between upper-extremity lean mass and handgrip strength (0.75, $P < 0.001$). The correlation between lower-extremity lean mass and strength values was significant, but weak (0.14, $P < 0.01$).

BMD and Muscle Strength Results

Table 2 displays correlations between BMD and muscle strength. In the lower extremity, there were significant but weak correlations between muscle strength and BMD. The BMD correlation values for plantar flexion ranged 0.113 to 0.118 in the left extremity and 0.049 to 0.099 in the right extremity. Knee extension BMD correlation ranged 0.169 to 0.235 in the left leg and 0.233 to 0.286 in the right leg. The plantar dorsiflexion BMD correlation value for the left foot was 0.087, and for the right it was 0.020. These correlations were determined at varying degrees for each position. These values were substantially lower than values for handgrip, demonstrating that the lower-extremity BMD was not as dependent on muscle strength, in contrast to findings in the upper extremity. Much stronger correlations existed between upper-extremity BMD and handgrip strength. The correlation coefficients for left and right handgrip were 0.700 and 0.696, respectively.

^eSAS Institute, 100 SAS Campus Dr, Cary, NC 27513.

Table 2 and figure 2 show the results of the final multiple variable regression models. After adjusting for covariates (ie, age at diagnosis, sex, time since diagnosis, height, weight, osteoporosis medication use, cranial radiation, and treatment related glucocorticoid dose), in the lower extremities, there were significant but modest associations between BMD and muscle strength, with R^2 values ranging 0.33 to 0.40 (see table 2). Stronger associations were evident in the upper extremities. The model containing handgrip strength, age at diagnosis, sex, time since diagnosis, height, weight, osteoporosis medication use, cranial radiation, and treatment-related glucocorticoid dose, explained 56% of the variation in corresponding BMD (left-hand $R^2 = 0.558$; right-hand $R^2 = 0.560$).

DISCUSSION

Adult survivors of ALL are at increased risk for skeletal morbidities, including BMD deficits.³ We investigated the relationship between muscle strength and BMD to determine if increased muscle strength had a positive effect on BMD in ALL survivors. Our results demonstrate a strong, significant association between muscle strength and BMD in the upper extremities of ALL survivors, as well as modest correlations between muscle strength and BMD in the lower extremities. These data are relevant to the development of interventions directed at optimizing bone health in adults at risk of BMD deficits after treatment of childhood cancer.

Our upper-extremity findings are important because wrist fractures are common in elderly persons with low BMD.³⁰ These findings agree with several other studies that demonstrated a positive relationship between lean mass, muscle strength, and BMD of the arms in both healthy^{31,32} and other populations with chronic disease.^{33–35} Marin et al³¹ found that among all applied physical tests, lean mass or handgrip strength most significantly related to BMD across all analyzed sites in healthy, physically active, postmenopausal women.³¹ Di Monaco et al³² also observed that handgrip strength was a strong independent predictor of BMD at the distal radius in postmenopausal women. Notably, these study populations differ from ours in health status and age as they evaluated healthy older women, while the SJLIFE cohort includes younger subjects of both sexes with a variety of residual morbidities from ALL and its treatment.

Jorgensen,³³ Pang,³⁵ and colleagues investigated upper-extremity BMD and strength in stroke patients with hemiparesis and a significant lack of function. Both studies demonstrated that decreased muscle strength and physical inactivity resulted in a reduction in BMD by as much as 27%.³³ Comparable to our study cohort of long-term ALL survivors, these studies evaluated a poststroke population who also have reduced physical ability and decreased muscle strength compared with that expected in a healthy population.^{7,14,16} Iwamoto et al³⁴ found that the decrease in arm function and disuse of the wrist were significant determinants of BMD in a group of postmenopausal women with rheumatoid arthritis. This latter patient population resembles our patient population in that both groups received corticosteroid treatment, and both possess increased risk for a decrease in physical activity/muscular strength secondary to disease sequelae.

Our lower-extremity findings support previous literature describing the associations between muscle strength and BMD in the lower extremities of both healthy and diseased populations.^{36–38} Muscle strength is important; however, BMD in the lower extremities typically correlates more strongly with body mass^{33,39–43} than with actual muscle strength. Among their cohort of 54 healthy adolescent girls, Witzke et al³⁷ observed that lean mass and leg power best predicted BMD, while leg strength was not a significant contributor. Binkley et al⁴² also found that lean leg mass had the highest while muscle strength (measured by muscle force) had the lowest correlation with BMD in prepubertal boys and

girls. Both study populations were significantly younger and relatively healthier than the SJLIFE cohort; thus, their BMD values had not yet reached their peak values as in our cohort. However, their results were similar to those of our SJLIFE cohort in that muscle strength did influence BMD, though weak in comparison to muscle mass. Taaffe et al³⁹ found that muscle strength in healthy older adults aged 70 to 79 years contributed significantly to BMD; however, its effect was diminished when lean mass was considered in the analysis. These findings are very similar to the results from lower-extremity assessments of the SJLIFE cohort, though we did not specifically adjust for lean mass. Taaffe³⁹ suggested that the decreased effect of muscle strength in comparison to lean mass was to be expected because muscle strength is proportional to the cross-sectional area of muscle. As a result, once the results are adjusted for lean mass, muscle strength contributes little to BMD.

Pang,³⁶ Lazoura,³⁸ and colleagues studied the consequences of hemiparesis in the lower extremities secondary to stroke. They found that while muscle strength could predict BMD, lean mass had a stronger effect on BMD. These findings were likely secondary to disuse and the associated lack of regular weight bearing and movement (walking) in the lower limbs (after stroke). It is possible that losses in strength and BMD in our ALL survivors was also related to decreased physical activity during treatment. Although we do not have information on the fitness or physical activity levels of our survivors during ALL therapy, this speculation is based on previous reports of either fitness levels or physical activity and bone density among very small, more current, cohorts of children evaluated during or soon after treatment for ALL. San Juan et al⁴⁴ reported peak maximum oxygen uptake levels lower than predicted (for age and sex) among 7 children during the maintenance phase of chemotherapy for ALL. Tillman et al⁴⁵ observed a significant association between low levels of self-reported physical activity and low lumbar BMD in a cohort of 31 young ALL survivors (mean age, 10.7y).

Our findings support Wolff's Law, which describes bone development in response to stresses placed on it. Stress occurs on long bones when tension, compression, bending, or stretch forces act on opposed sides of the bone.⁴⁶ Strain on bone occurs, both when the bone is in a weight-bearing position, and when muscle pulls on it. Bone deposition occurs when mechanical strain is intensified (eg, during periods of increased physical activity).²¹ When mechanical strain is lessened (eg, periods of immobility or disability), bone resorption occurs.²¹ Because upper extremities typically do not bear weight, BMD in the arms is more dependent on muscle strength than BMD in the legs, where weight bearing also contributes to the strain placed on bone.

Our study adds to the literature indicating the positive association between increased BMD and overall fitness among ALL survivors. However, previous investigators have focused more on cardiopulmonary fitness or activity levels rather than specifically on muscular strength. One group of investigators⁹ reported a positive association between exercise capacity ($r = 0.44$) and percent bone mineral content at the hip among 55 survivors of ALL and other childhood malignancies. Our previous work⁴⁷ also documented a positive association between physical activity levels and BMD among 57 ALL survivors. Studying a smaller cohort of childhood ALL survivors aged 20 to 32 years, Jarfelt et al⁴⁸ found that physical fitness training from an early point in the treatment and/or recovery period was the most important factor in developing and maintaining BMD.

Study Limitations

There are some limitations in this study. First, our participation rate was under 100%. The survivors who agreed to take part in the study may have been more likely than those who did not participate to be concerned about their health; they may have lifestyle habits that could positively impact their BMD and muscle strength. For example, SJLIFE participants may be

more likely to exercise, be nonsmokers, and take vitamins. Second, survivors who were too obese for the imaging table were excluded from the study. Because BMD is positively correlated with weight, excluding these survivors may have resulted in an underestimation of the true association between muscle strength and BMD. Additionally, compliance with oral glucocorticoid therapy could not be verified for individual patients and was assumed. Scheduled dose of glucocorticoids was used as a surrogate. Finally, over two-thirds of our study population was treated with cranial radiation, a treatment that is used sparingly among children with ALL on modern protocols. Our data may not apply to future survivors of childhood onset ALL.

CONCLUSIONS

We found an association between muscle strength and BMD in the extremities for the first time in a large cohort of long-term survivors of childhood ALL. It appears this association is more important in the upper than in the lower extremities, where the effects of load bearing likely diminish the effect of muscle strength on BMD. These results offer promise that a muscle strengthening intervention may improve bone health among ALL survivors, particularly in those who have BMD deficits in the upper extremities. Including a DEXA scan with reports of both whole body and forearm BMD *z* scores as part of cancer survivor medical follow-up will help provide useful information for the clinician.

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List of Abbreviations

ALL	acute lymphoblastic leukemia
BMD	bone mineral density
DEXA	dual energy x-ray absorptiometry
IGF-1	insulin-like growth factor 1
SJLIFE	St Jude Lifetime Cohort

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Fig 1.

Recruitment details of ALL survivors. Seventy-one declined any participation, 93 agreed to survey only or home-health evaluation conducted by Examination Management Services Inc, and 38 declined, but agreed to be contacted in 1 year.

Fig 2.

Association between handgrip strength (kg) and arm BMD (g/cm^3). Variation in (A) left and (B) right handgrip strength explains 56% of the variation in corresponding BMD when adjusted for age at diagnosis, sex, time since diagnosis, height, weight, osteoporosis medication use, cranial radiation, and scheduled glucocorticoids dose: left-hand adjusted $R^2 = 0.558$ and right-hand adjusted $R^2 = 0.560$.

Table 1**Subject Characteristics**

Characteristic	Descriptive Statistics
Sex [*]	
Women	261 (53)
Men	232 (47)
Race [*]	
White	460 (93)
Other	33 (7)
Age at examination (y)	
Mean $\pm$ SD	33.3 $\pm$ 7.1
Median (range)	32.6 (20.4 to 54.4)
Age at diagnosis (y)	
Mean $\pm$ SD	6.3 $\pm$ 4.3
Median (range)	5.0 (0.2 to 18.8)
Time since diagnosis	
Mean $\pm$ SD	27.7 $\pm$ 7.5
Median (range)	27.2 (12.7 to 46.5)
Height (cm)	
Mean $\pm$ SD	166.0 $\pm$ 11.0
Median (range)	166.3 (138.5 to 194.0)
Weight (kg)	
Mean $\pm$ SD	81.4 $\pm$ 19.3
Median (range)	81.1 (37.3 to 132.1)
IGF-I (z score)	
Men	232 (47)
Mean $\pm$ SD	-1.6 $\pm$ 1.9
Median (range)	-1.2 (-8.4 to 3.0)
Premenopausal women	213 (43)
Mean $\pm$ SD	-2.0 $\pm$ 2.0
Median (range)	-1.6 (-7.7 to 1.9)
Postmenopausal women	48 (10)
Mean $\pm$ SD	-3.3 $\pm$ 2.1
Median (range)	-3.4 (-6.9 to 0.1)
Limb Surgery [†]	
Lower extremity	30 (6)
Upper extremity	11 (2)
Osteoporosis medication	16 (3)
Cranial radiation	347 (70)
Glucocorticoids [‡] (mg/m ²)	
Mean $\pm$ SD	6,183 $\pm$ 5169
Median (range)	7610 (1120 to 23,632)

Characteristic	Descriptive Statistics
Methotrexate (mg/m ²)	
Mean ± SD	7842 ± 7719
Median (range)	4944 (219.6 to 32,014)
Cyclophosphamide (mg/m ²)	
Mean ± SD	10,614 ± 6645
Median (range)	9498.4 (300.0 to 38,487)

NOTE. N = 493.

* Discrete data, sex, and race are presented as n (%).

[†] Including amputation, arthroplasty, arthroscopy, chondroplasty, decompression, hemiarthroplasty, fasciotomy, fixation, fusion, reconstruction, and repair.

[‡] Scheduled dose by treatment protocol.

Table 2Association* and Correlations Between Muscle Strength and BMD (g/cm³)

Muscle Strength by BMD of Limb	<i>R</i> ²	<i>P</i>	Pearson Correlation Coefficient	<i>P</i>
Left-leg BMD				
60°/s plantar flexion (Nm/kg)	0.322	.105	0.118	.011
90°/s plantar flexion (Nm/kg)	0.322	.109	0.113	.015
60°/s knee extension (Nm/kg)	0.323	.243	0.169	<.001
180°/s knee extension (Nm/kg)	0.332	.011	0.235	<.001
300°/s knee extension (Nm/kg)	0.335	.003	0.200	<.001
60°/s dorsiflexion (Nm/kg)	0.316	.719	0.087	.062
Right-leg BMD				
60°/s plantar flexion (Nm/kg)	0.379	.111	0.099	.034
90°/s plantar flexion (Nm/kg)	0.379	.287	0.049	.299
60°/s knee extension (Nm/kg)	0.405	<.001	0.286	<.001
180°/s knee extension (Nm/kg)	0.400	<.001	0.267	<.001
300°/s knee extension (Nm/kg)	0.406	<.001	0.233	<.001
60°/s dorsiflexion (Nm/kg)	0.377	.731	0.020	.661
Left-arm BMD				
Left handgrip (kg)	0.558	<.001	0.700	<.001
Right-arm BMD				
Right handgrip (kg)	0.560	<.001	0.696	<.001

* Adjusted for age at diagnosis, sex, time since diagnosis, height, weight, osteoporosis medication use, cranial radiation, and scheduled glucocorticoid dose.