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ORIGINAL RESEARCH

Effects of a Bone-Strengthening Exercise Intervention on Bone Health in Pediatric Cancer Survivors: A Randomized Controlled Trial

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Abstract

Objectives: To investigate the effects of a 9-month online bone-strengthening exercise intervention on the femoral neck areal bone mineral density (aBMD) *z* score and other bone health parameters.

Design: Assessor-blinded randomized controlled trial with 2 parallel arms.

Setting: Sport and Health University Research Institute (iMUDS), Granada, Spain.

Participants: A total of 116 pediatric cancer survivors (N=116) aged 6-18 years (12.1±3.3y; 42% girls).

Interventions: Before the intervention, all participants received dietary counseling on calcium and vitamin D intake. The exercise group performed a 9-month periodized video-recorded bone-strengthening exercise intervention based on squats and jumps (3-4 d/wk for 10-20 min/session) at home.

Main Outcome Measures: Primary (femoral neck aBMD [g/cm^2]) and secondary outcomes (aBMD and bone mineral content [g]) were measured using dual-energy x-ray absorptiometry at the hip regions (femoral neck and total hip), total body, and lumbar spine (mean of L1-L4) at baseline and 9-month postintervention.

Results: No between-group differences in femoral neck aBMD *z* score (Cohen d=−0.08; *P*=.706) and aBMD *z* score outcomes were observed after the intervention. However, the intervention showed small effect sizes on the total hip, with a borderline nonsignificant improvement in aBMD *z* score (Cohen d=0.35; *P*=.054) and a significant improvement in bone mineral content *z* score (Cohen d=0.38; *P*=.039).

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Conclusions: The 9-month online bone-strengthening exercise intervention did not increase the femoral neck aBMD *z* score; however, it improved the overall bone mineral content *z* score at the hip in young pediatric cancer survivors.
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Cancer treatments in early life increase the risk of long-term health complications,[1] including low areal bone mineral density (aBMD),[2] prevalent in approximately two-thirds of survivors.[3] Nonpharmacologic treatments, including exercise,[4] improve aBMD in children without pediatric cancer if exercise training principles (ie, frequency, intensity, time, type, volume, and progression) are appropriately followed. However, randomized controlled trials (RCTs) in this population[5] targeting bone outcomes such as femoral neck aBMD, a key outcome in the diagnosis of osteoporosis during adulthood,[6] are limited. According to the International Society for Clinical Densitometry,[6] the World Health Organization international reference standard for osteoporosis diagnosis is based on this region. In addition, previous clinical risk fracture models, such as the Fracture Risk Assessment tool,[7] have been extensively used, including femoral neck aBMD, apart from prior clinical risk factors of fractures and age, which shows the clinical relevance of this region.

Prior exercise interventions in young pediatric cancer survivors have been ineffective,[5] which could be attributed to the short duration of trials (3mo),[8] inclusion of nonosteogenic exercises (aerobic exercise),[9] or a microgravity environment (swimming pools).[8] Moreover, meeting the exercise frequency and intensity required to improve bone outcomes is challenging for children during treatment.[10] Therefore, exercise-based RCTs specifically designed to improve bone health after pediatric cancer are required. This RCT aimed to investigate the effects of a 9-month online bone-strengthening exercise intervention on femoral neck aBMD *z* scores (primary outcome) and other bone health parameters (secondary outcomes) in young pediatric cancer survivors. We hypothesized that this intervention improves bone health at relevant clinical regions at the hip (ie, femoral neck and total hip) in this population, rather than overall total body or upper limbs.[11]

Methods

Study design

The REBOTA-Ex parallel-group RCT (part of the iBoneFIT project) was approved by the Ethics Committee on Human Research (reference: 4500, December 2019), followed the ethical guidelines of the Declaration of Helsinki (revised version 2013), and was registered on isrctn.com (reference: isrctn61195625, April 2, 2020).[12] The study followed the consolidated standards of reporting trials reporting guidelines (supplemental table S1, available online only at http://www.archives-pmr.org/). All research processes were conducted following the Singapore Statement on Research Integrity.[13]

List of abbreviations:

BMC	**bone mineral content**
DXA	**dual-energy x-ray absorptiometry**
RCT	**randomized controlled trial**

Study participants

Pediatric cancer survivors aged 6-18 years, diagnosed at least 1 year prior to enrolment, who had received radiotherapy and/or chemotherapy but were not currently undergoing cancer treatment were included. Exclusion criteria included simultaneous participation in another study placing participants at any additional risk, discomfort or affect the results of both studies; previous diagnosed anorexia nervosa/bulimia; known pregnancy and/or known alcohol and drug abuse; children requiring chronic oral glucocorticoid therapy; having an injury that may affect daily life activities and can be aggravated by exercise; and having a lower limb prosthesis that prevents bone assessment. Because of COVID-19 restrictions, data collection was performed in 2 phases: (1) October 2020-November 2021 and (2) December 2021-January 2023. Sample size was calculated based on an expected effect size of 0.25 for the change in femoral neck aBMD (key outcome in the diagnosis of osteoporosis),[6] with an α level of 0.05 and power of 80%. Considering a 20% loss to follow-up and potential subgroup analysis by age, a minimum of 116 participants was required (N=58 each in the exercise and control groups).

Randomization and blinding

After baseline assessments, the participants were randomized (1:1) to the exercise or control group using SAS software[a] (version 9.1, SAS Institute Inc) by an external partner who was not involved in the recruitment, enrolment, evaluation, or exercise intervention. Preparation for this randomization was done prior to baseline assessments. Although outcome assessors were blinded to group allocation, participants could not be blinded because of the nature of the exercise intervention.

Intervention

The exercise group performed periodized online bone-strengthening exercise interventions at home. Sessions were video-recorded and delivered to participants every 2 weeks and included a total of 7296 squats/jumps (2000 squats and 5296 jumps) in 136 sessions, each lasting for 10-20 minutes. The intensity progressively increased in volume (3-4 sets, 10-20 repetitions, and 3-4 sessions per wk) during the intervention phase (fixed protocol). The intervention was divided into 3 phases with different durations and impact loading. Phase 1 corresponded to the first 8 weeks of the exercise intervention, and participants performed body mass-based squats. Phase 2 lasted for 12 weeks, and the participants performed squat jumps. Phase 3, the longest phase, lasted 16 weeks, and the participants performed countermovement jumps. Additionally, the exercise intervention incorporated 5 behavior change techniques and a gamification design (featuring points and rankings) to maintain participants' engagement and adherence,

especially for our growing population.[14-16] After completing each week of every phase of the intervention, each participant had an avatar displayed in Genially, a website where they could monitor their progress with the current position of their avatars. As soon as they reached the end of each phase, they had to achieve an objective and were challenged to accomplish different tasks, such as bringing a friend or family member to work out with them, and also received information on the health-related benefits of exercise, specifically the different osteogenic physical activities.

Educational leaflets and infographics based on the current recommendations for calcium and vitamin D[17] intake were delivered to all participants before the intervention. The participants in the control group continued their usual routines and were offered the same online bone-strengthening exercise intervention at the end of the trial (waitlist control group).

Adherence

The intervention was remotely monitored using a diary provided at baseline. The minimum adherence allowed during the first phase of the intervention without justified reasons was 50%; however, the overall adherence at 9 months was required to be 70% (completion of 95/136 sessions). If a participant did not complete 70% of the intervention at the end of the 9 months but was able to reach 70% within 2 additional weeks, the exercise intervention was extended. To encourage adherence, participants were contacted monthly by the research staff to review the number of sessions completed and to provide problem-solving strategies.

Outcomes

Primary (femoral neck aBMD [g/cm^2]) and secondary outcomes (aBMD and bone mineral content [BMC, g]) were measured using dual-energy x-ray absorptiometry (DXA) at the hip regions (femoral neck and total hip), total body (less head), and lumbar spine (mean of L1-L4) at baseline and 9-month follow-up. Scanning was performed using a single DXA scanner (Hologic Series Discovery QDR) and analyzed using APEX software (version 4.0.2). The device was calibrated daily using a lumbar spine phantom. The participants were instructed to remain still in the supine position during scanning.[6] All DXA scans were analyzed by a licensed and experienced researcher. The coefficient of variation for DXA in the pediatric population ranges from 1.0% to 2.9%, depending on the body region.[18] Using international reference data from the Bone Mineral Density in Childhood Study,[19] age-, sex-, and race-specific aBMD and BMC z scores were calculated and used as outcome variables.

Anthropometric and clinical variables

Body weight (kg), height (cm), and body mass index (kg)/stature (m^2) were obtained using standard procedures. Additionally, age- and sex-specific body mass index z scores and categories were calculated using the international reference data for the pediatric population according to the World Obesity Federation.[20] Somatic maturity was measured by predicting the years before or after peak height velocity using validated algorithms for boys and girls.[21] Participants were categorized as prepubertal (<-1y from peak height velocity) and peri/postpubertal (>-1y from peak height velocity).[22] Vitamin D status was estimated using a validated food frequency questionnaire.[23] Medical records were reviewed for serum calcium levels (mg/dL), diagnosis, time from treatment completion to baseline data collection, and treatment exposure (radiotherapy, chemotherapy, and/or surgery, alone or in combination).

Statistical analysis

Primary and secondary outcomes were assessed using both intention-to-treat analysis, including all participants as originally randomized, and the per-protocol analysis, including only adherent participants (those completing at least 95/136 sessions) with assessment at both time points (available in the supplementary online materials). Missing data were not imputed,[24,25] because baseline values were considered as part of the outcome vectors, and all participants with at least 1 assessment were included in the analyses.[26] We considered missing data for postintervention outcomes to be missing at random because there were no significant differences between dropouts and nondropouts (supplemental table S2, available online only at http://www.archives-pmr.org/).

Intervention effects on primary and secondary outcomes were analyzed using a constrained longitudinal data analysis with linear outcomes, constraining the baseline means of the outcome measure to be the same in both groups.[26] The model included fixed effects for time (2 levels), treatment (coded 0 for all groups at baseline and 1 or 0 at the 9-mo follow-up for the exercise and control groups, respectively), and a unique participant identifier as a random effect. The effects of time and time$\times$group interactions were also included in the model. Data are presented as within-group mean changes and between-group mean change differences with 95% CI. Effect sizes were calculated according to Cohen d formula, interpreted according to the standard criteria: $\sim$0.2, 0.5, and 0.8 standard deviations for small effect, medium effect, and large effect sizes, respectively.[27] The LMMstar package was used for analysis,[28] and all statistical analyses were performed using R statistical software[b] (version 4.4.0; R Foundation for Statistical Computing). All P values were obtained from 2-sided tests, and P values $< .05$ indicated statistical significance. Additionally, multiple testing corrections were applied to the primary and secondary outcomes, and subgroup analyses were performed using the false discovery rate method proposed by Benjamini and Hochberg.[29]

Interpretation of the intervention effect assessments was based not only on statistical significance but also on a practical-benefit approach, emphasizing and reporting unadjusted values that are intuitive to human judgment and readily replicable, considering the design and methods used in this study.[30,31] However, posteriori-planned subgroup analyses were performed separately by sex (boys and girls), somatic maturity (prepubertal and peri/postpubertal), and low aBMD/BMC at baseline (z score < -1 and z score ≥ -1), in addition to a priori subgroup analyses by age (6-11 and 12-18y).

Deviations from the original protocol

Although we originally intended to analyze primary and secondary outcomes using analysis of covariance, we were advised to use a constrained baseline longitudinal analysis via a linear mixed model because it is currently being considered the standard method and handles missing values reasonably well, adopting this for primary analyses.[26] Nevertheless, in secondary analyses, we also provide the per-protocol analysis using both analysis of covariance and a constrained baseline longitudinal analysis via a

linear mixed model, and the results are consistent (supplemental tables S3 and S4, available online only at http://www.archives-pmr.org/).

Results

Study participants

Among the 196 invited participants, 116 provided consent (recruitment rate: 59.2%) (fig 1). In the exercise group, 13 participants did not complete the postintervention bone health evaluation, and 9 did not meet the adherence requirements. In the control group, 4 participants did not complete the postintervention bone health evaluation. The median (interquartile range) adherence in the exercise group was 93.8% (9.4), 90.9% (19.3), and 73.3% (34.2) in the first, second, and third phases, respectively, resulting in a total adherence rate of 87.4% (12.7). All 116 participants were included in the intention-to-treat analysis, and 90 (77.6%) were included in the planned per-protocol analysis. No significant differences, except for radiotherapy exposure, were observed between dropouts and nondropouts (P=.014) (supplemental table S2).

The baseline characteristics of the participants are listed in table 1. Of the included participants, 58 were randomized to the exercise group (mean [SD] age: 11.7 [3.2]y [range: 6.4%-17.7%]; 37.9% were girls), and 58 were randomized to the control group (mean [SD] age: 12.5 [3.5]y [range: 6.4-18.0]; 46.6% were girls). The proportion of participants exposed to radiotherapy was comparable between the groups (27.6%). The aBMD and BMC z scores were slightly higher in the exercise group than in the control group for all outcomes. Acute lymphoblastic leukemia was the most common cancer type (39.7% and 37.9% in the exercise and control groups, respectively [supplemental table S5, available online only at http://www.archives-pmr.org/]).

Changes in aBMD and BMC *z* scores

Table 2 shows within- and between-group differences in primary and secondary outcomes from baseline to the end of intervention. No between-group differences were observed in femoral neck aBMD z score (Cohen d=−0.08; P=.706) or other aBMD z score outcomes. However, the intervention had a small-sized borderline nonsignificant effect on total hip aBMD z score (Cohen d=0.35; P=.054) and a significant effect on total hip BMC z score (Cohen d=0.38; P=.039). No other between-group differences were observed. Compared with the control group, the exercise group

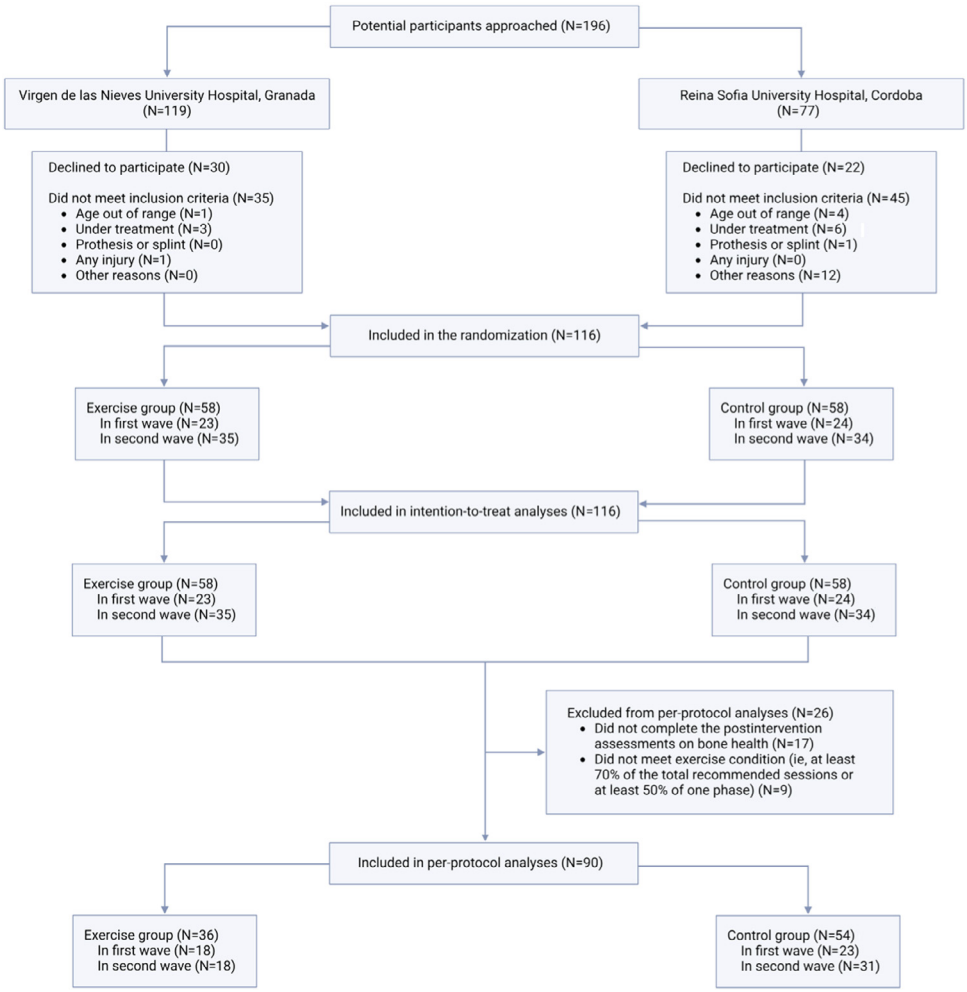


Fig 1 Flowchart of participant selection.

Table 1 Baseline characteristics of the included participants.

Variables	Total	N	Exercise Group	N	Control Group	N
Sex (girls, %)	42.2	116	37.9	58	46.6	58
Age (y)	12.1 (3.3)	116	11.7 (3.2)	58	12.5 (3.5)	58
Body weight (kg)	46.6 (18.0)	116	46.9 (17.9)	58	46.3 (18.3)	58
Height (cm)	147.5 (17.1)	116	147.2 (16.7)	58	147.7 (17.6)	58
Body mass index *z* score	0.9 (1.1)	116	1.0 (1.2)	58	0.8 (1.1)	58
Body mass index (categories, %)						
Underweight	3.5	4	3.4	2	3.4	2
Normal weight	61.2	71	55.2	32	67.2	39
Overweight	20.7	24	24.1	14	17.2	10
Obese	14.6	17	17.2	10	12.1	7
Years from peak height velocity	−0.8 (2.7)	116	−1.0 (2.6)	58	−0.5 (2.8)	58
Vitamin D deficiency (yes, %)	53.2	111	50.0	56	56.4	55
Calcium (mg/dL)	9.8 (0.5)	103	9.8 (0.6)	53	9.9 (0.5)	50
Time from cancer treatment completion (y)	5.0 (3.8)	113	4.5 (3.5)	57	5.6 (4.0)	56
Radiotherapy exposure (yes, %)	27.6	116	27.6	58	27.6	58
aBMD *z* score						
Femoral neck	−0.2 (1.4)	115	−0.1 (1.5)	58	−0.3 (1.3)	57
Total hip	0.1 (1.3)	115	0.2 (1.3)	58	0.1 (1.3)	57
Total body	−0.2 (1.4)	116	0.0 (1.4)	58	−0.4 (1.4)	58
Lumbar spine	−0.1 (1.3)	116	0.1 (1.2)	58	−0.3 (1.4)	58
BMC *z* score						
Femoral neck	−1.3 (1.5)	115	−1.2 (1.5)	58	−1.4 (1.5)	57
Total hip	0.4 (1.4)	115	0.5 (1.4)	58	0.3 (1.5)	57
Total body	−0.5 (1.3)	116	−0.3 (1.1)	58	−0.7 (1.4)	58
Lumbar spine	−0.5 (1.3)	116	−0.2 (1.0)	58	−0.7 (1.5)	58

Data are presented as the means (standard deviations) or frequencies (%), as indicated. Age- and sex-specific body mass index *z* scores and categories were presented using the international reference data for the pediatric population according to the World Obesity Federation.[18] Additionally, age-, sex-, and race-specific aBMD and BMC *z* scores at each site are presented using the international reference data from the Bone Mineral Density in Childhood Study.[17] Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content.

demonstrated small-sized effects ranging from 0.26 to 0.28 (P=.168-.124) for the femoral neck, total body, and lumbar spine BMC *z* scores. Estimated means at constrained baseline and 9-month follow-up in the aBMD and BMC *z* score outcomes are presented in figure 2. Subgroup analyses (available in the supplementary online materials, supplemental fig S1, available online only at http://www.archives-pmr.org/) revealed descriptive and exploratory findings based on the interactions of age (lumbar spine BMC *z* score), sex (femoral neck, total hip, total body, and lumbar spine BMC *z* score), somatic maturity (lumbar spine BMC *z* score), and baseline bone health values (total hip BMC *z* score).

In the per-protocol analysis, the findings for aBMD *z* score outcomes were consistent with those from the intention-to-treat analyses (supplemental table S4). However, the effect sizes of the intervention on BMC outcomes increased in the per-protocol compared with the intention-to-treat analyses (Cohen d=0.42-0.43; P=.050-.043) for the femoral neck, total body, and lumbar spine, and remained similar (Cohen d=0.39; P=.057) for the total hip. Using this approach, the estimated means at constrained baseline and 9-month follow-up in the aBMD *z* score outcomes and raw individual changes in the total hip and femoral neck aBMD *z* scores from baseline to 9-month follow-up were analyzed (supplemental fig S2, available online only at http://www.archives-pmr.org/). No adverse events were reported.

Adverse events

There were no reported adverse events regarding the intervention.

Discussion

Our findings indicated that the 9-month online bone-strengthening exercise intervention did not significantly increase the femoral neck aBMD *z* score; however, it improved the overall BMC *z* score at the hip in young pediatric cancer survivors. Notably, among those who completed the minimum recommended number of exercise sessions (per-protocol analysis), nearly medium-sized effects were observed for the femoral neck BMC *z* score.

Our intervention was not effective at improving femoral neck aBMD *z* score, which is against the initial hypothesis. Contrary to a previous systematic review of children and adolescents without pediatric cancer, beneficial effects of plyometric exercise-based interventions were found on femoral neck aBMD.[4] However, previous nonosteogenic exercise interventions in young pediatric cancer survivors[8,9] demonstrated similar nonsignificant effects on femoral neck aBMD *z* scores and aBMD, suggesting that this specific region could be less responsive after cancer treatments. A recent systematic review and meta-analysis[32] interestingly found that the decline in aBMD *z* scores was more pronounced at the femoral neck than at other regions, such as the lumbar spine, and hence, this could partially explain the discrepancy with the initial hypothesis. Lean muscle mass loss and consequent reduced loading following impacts (ie, jumps) could also affect bone mass development in this region, because, according to Frost's mechanostat theory, bigger muscles exert higher tensile forces on the bones they attach.[33] Another reason could be that the intensity of our intervention may not have been enough for our sample, compared with the studies included

Table 2 Baseline, within-group changes (baseline to 9-mo follow-up), and between-group differences (exercise vs control) in the aBMD and BMC *z* score outcomes (intention-to-treat analysis).

Outcomes	Exercise Group		Control Group		Between-group Differences		
	Mean (95% CI)	Change %[Ψ]	Mean (95% CI)	Change %[Ψ]	MD (95% CI)	Effect size	$P^{\dagger}$
Femoral neck aBMD *z* score							
Baseline	−0.20 (−0.46 to 0.06)	NA	−0.20 (−0.46 to 0.06)	NA	NA	NA	NA
Changes at 9-mo	0.11 (−0.05 to 0.28)	4.11	0.15 (0.00-0.30)	5.48	−0.04 (−0.22 to 0.15)	−0.08	.706
Total hip aBMD *z* score							
Baseline	0.14 (−0.10 to 0.38)	NA	0.14 (−0.10 to 0.38)	NA	NA	NA	NA
Change at 9-mo	0.22 (−0.01 to 0.46)	6.10	−0.03 (−0.25 to 0.18)	−3.66	0.26 (0.00-0.52)	0.35	.054
Total body aBMD *z* score							
Baseline	−0.19 (−0.44 to 0.06)	NA	−0.19 (−0.44 to 0.06)	NA	NA	NA	NA
Changes at 9-mo	0.03 (−0.16 to 0.23)	3.80	−0.06 (−0.24 to 0.12)	−3.80	0.09 (−0.13 to 0.31)	0.15	.422
Lumbar spine aBMD *z* score							
Baseline	−0.07 (−0.32 to 0.18)	NA	−0.07 (−0.32 to 0.18)	NA	NA	NA	NA
Changes at 9-mo	−0.05 (−0.19 to 0.08)	−4.11	−0.02 (−0.14 to 0.10)	−4.11	−0.04 (−0.19 to 0.12)	−0.07	.642
Femoral neck BMC *z* score							
Baseline	−1.27 (−1.55 to −0.99)	NA	−1.27 (−1.55 to −0.99)	NA	NA	NA	NA
Changes at 9-mo	0.30 (−0.08 to 0.69)	10.51	0.00 (−0.36 to 0.36)	7.25	0.30 (−0.13 to 0.73)	0.26	.168
Total hip BMC *z* score							
Baseline	0.40 (0.14-0.66)	NA	0.40 (0.14-0.66)	NA	NA	NA	NA
Changes at 9-mo	0.39 (0.00-0.77)	14.83	−0.06 (−0.42 to 0.30)	−8.66	0.45 (0.02-0.87)	0.38	**.039**
Total body BMC *z* score							
Baseline	−0.49 (−0.73 to −0.25)	NA	−0.49 (−0.73 to −0.25)	NA	NA	NA	NA
Changes at 9-mo	0.10 (−0.07 to 0.27)	8.52	−0.04 (−0.20 to 0.12)	−7.08	0.14 (−0.06 to 0.33)	0.26	.171
Lumbar spine BMC *z* score							
Baseline	−0.45 (−0.68 to −0.21)	NA	−0.45 (−0.68 to −0.21)	NA	NA	NA	NA
Changes at 9-mo	0.11 (−0.06 to 0.28)	9.21	−0.04 (−0.19 to 0.12)	−7.07	0.15 (−0.04 to 0.34)	0.28	.124

The results are presented as the mean change from baseline for each group and the mean difference between the groups. Data were analyzed using constrained longitudinal data analysis with linear outcomes, assuming that the baseline means of the outcome measure were identical between the groups. Age-, sex-, and race-specific aBMD and BMC *z* scores at each site are presented using the international reference data from the Bone Mineral Density in Childhood Study.[17] Effect sizes were calculated using Cohen d formula. Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content; NA, not applicable.

Significant values ($P<.05$) are highlighted in bold.

[Ψ] The percentage change (9-mo follow-up−baseline values/baseline values×100) was calculated from the raw values (g/cm^2 or g).

[†] *P* values indicate between-group indicate between-group differences based on the aBMD and BMC *z* score outcomes.

in a previous systematic review of children and adolescents.[4] Moreover, the lack of supervision in our study involving growing children may have affected its effectiveness. In particular, supervision can ensure continuous engagement, immediate feedback, motivation, real compliance, and potential intensity adjustments in this population.

The small-sized effects on the total hip and femoral neck BMC *z* scores (intention-to-treat and per-protocol analyses, respectively) in our study were consistent with those observed in previous meta-analyses on BMC outcomes in children and adolescents.[34,35] Similar results were also found for aBMD outcomes,[34,35] but our findings on the total hip aBMD *z* score were small-sized borderline nonsignificant, and hence, they should be interpreted with caution. A recent similar meta-analysis in this population reported greater increases in BMC outcomes (standardized mean difference=1.348; 95% CI, 1.053-1.643) than in aBMD outcomes (0.640; 95% CI, 0.417-0.862).[36] BMC (g) is a measure of the amount of mineral present in the bone, and aBMD (g/cm^2) is a volumetric measure that accounts for both mineral quantity in grams and the area of the bone assessed by DXA. The optimal intervention duration to improve bone health in previous studies ranged from 8 to 12 months,[4] aligning with our study duration. In addition, the inclusion of behavioral change techniques, as in our intervention, is recommended,[14,16] which likely contributed to the high adherence rates (83%) among our study participants. Improvements observed during childhood may have important public health implications, such as reduction in osteopenia/osteoporosis risk,[37,38] subsequent fractures,[39] and the need for hospitalization, rehabilitation, or future disability in adulthood.[2]

Although our bone-strengthening exercise intervention was not effective in improving bone health in the total body, small-sized effects were observed on total body BMC *z* scores (per-protocol analysis). Plyometric exercises improved total body BMD and BMC outcomes in children and adolescents.[4] Mogil et al[40] observed substantial improvements in total body aBMD *z* scores in young pediatric cancer survivors following a low-magnitude, high-frequency mechanical stimulation for 1 year. This intervention was conducted 7 d/wk, with 2 sessions per day, each lasting 10 minutes. The positive outcomes may be attributed to the frequency (twice per day) and adequate intervention duration (1y). Consistent with our findings, a non-RCT evaluating the effects of a concurrent full-body exercise intervention for 6 months (3 d/wk, 55-60min per session) in survivors did not report significant effects on total body aBMD *z* scores.[9] Although our intervention was specifically designed to improve bone health following the training principles used in previous successful interventions in children and adolescents,[41,42] it lacked core and upper-body exercises that might have simulated muscle growth or activation and associated bone remodeling.[43] This could explain the small-sized effects (borderline) observed on lumbar spine BMC *z* scores (per-protocol analysis). Altogether, our findings suggest that bone adaptations may be site-specific because observed effects were mainly found at the hip region, which was our main target. However, given that our findings on the total hip aBMD *z* score were

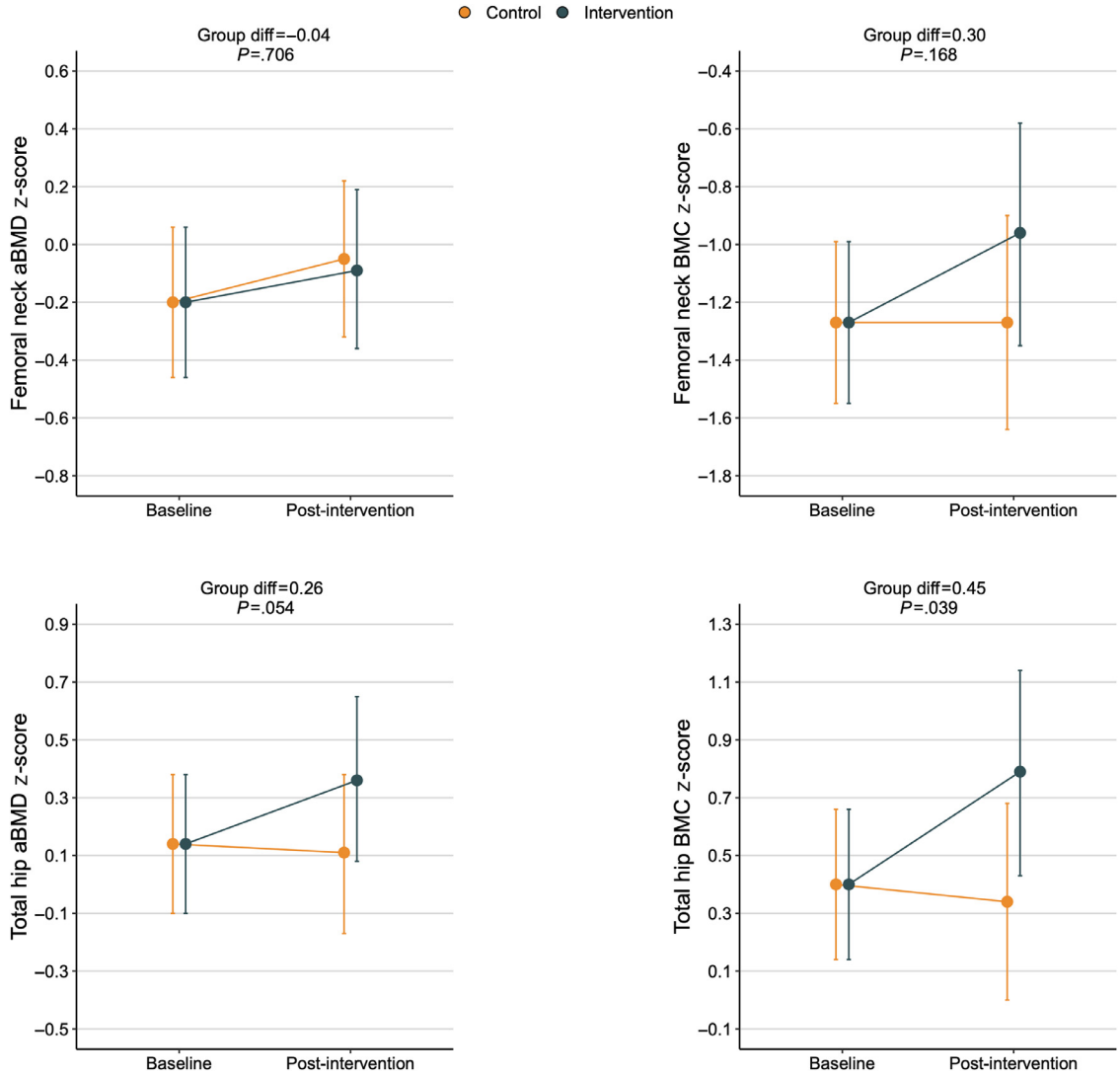


Fig 2 Estimated means at constrained baseline and 9-month postintervention follow-up in femoral neck and total hip aBMD and BMC *z* score outcomes. Error bars represent 95% CI. Data were analyzed using a constrained longitudinal data analysis with linear outcomes, assuming that baseline means of the outcome measure were identical between the groups (intention-to-treat analysis). Abbreviations: aBMD, areal bone mineral density; BMC, bone mineral content; diff, difference.

small-sized and borderline nonsignificant, clinical implications should be made with caution.

Study limitations

Our study had certain limitations, which should be considered while interpreting the results of this RCT. First, although adherence to the intervention was monitored using a monthly diary review, the exercise sessions were not supervised throughout the intervention. Supervision is key in exercise trials because it can provide immediate feedback and engagement with participants to adapt and personalize sessions according to them. Lack of session supervision can drastically affect the effectiveness of exercise because the individual's needs are not being considered (ie, technique limitations can affect intensity, leading to limited outcomes improvement). Nevertheless, parents provided necessary support when needed, and the research staff maintained frequent contact via chat groups. Notably, we observed higher positive effects among those who completed a minimum number of exercise sessions (per-protocol analysis). However, additional objective monitoring methods (ie, wearable sensors) could have provided more robust compliance data. Second, COVID-19 restrictions may have affected the efficacy of this RCT, increasing stress, anxiety, sedentary time, and decreasing motivation, diet quality, and sleep hygiene; however, we lack data to confirm this in our sample. Third, recruiting participants was challenging because of the rarity of pediatric cancer. The small and geographically dispersed population limited the final pool of eligible patients, and this is why another hospital outside of Granada was considered to be involved since the beginning. Future studies should consider evaluating the benefits of a similar bone-strengthening exercise intervention in survivors with low aBMD. Fourth, missing values at 9-month postintervention follow-up were considerably higher in the exercise group than in the control group, yet the percentage of missing values was low and there were no significant differences between dropouts and nondropouts, except for radiotherapy exposure. Fifth, although outcome assessors were blinded to group allocation, participants could not be blinded because of the nature

of the exercise intervention. Participants who were aware of receiving the exercise intervention may have been more motivated or inclined to report perceived improvements. Conversely, control participants might have underreported benefits because of expectations of receiving "less active" treatment. These expectancy effects could influence the outcomes, potentially inflating the effectiveness of the intervention.

Conclusions

Although the 9-month online bone-strengthening exercise intervention did not increase the femoral neck aBMD z score, it improved the overall BMC z score at the hip in young pediatric cancer survivors. This intervention seemed to be safe because no adverse events were reported. Further work needs to be done to determine whether modifications in our intervention (ie, supervision, full-body exercise sessions) could provide greater improvements in bone health.

Suppliers

a. SAS, version 9.1; SAS Institute.
b. R, version 4.4; R Core Team.

Authorship contributions/CRediT statements

A.M.-P.: Project administration, Investigation, Writing − Original draft. E.U.-G.: Conceptualization, Methodology, Project administration, Investigation, Writing − Review and editing. J.J.G.-C.: Project administration, Investigation, Writing − Review and editing. A.R.-S.: Project administration, Investigation, Writing − Review and editing. F.B.O.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. M.E.M.G.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. J.F.P.-G.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. F.J.L.-C.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. C.C.-S.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. V.M.-V.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. K.K.N.: Writing − Review and editing. J.R.R.: Conceptualization, Methodology, Funding acquisition, Writing − Review and editing. L.G.-M.: Conceptualization, Methodology, Project administration, Supervision, Funding acquisition, Writing − Original draft.

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Data statements

Data will be available on reasonable request.

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