Characteristics of Interventions to Improve Bone Health in Children With Cerebral Palsy: A Systematic Review

Brianna M. Liquori, MS; Mary E. Gannotti, PT, PhD; Deborah E. Thorpe, PT, PhD; Robyn K. Fuchs, PhD, FACSM

Shriners Hospitals for Children (Ms Liquori and Dr Gannotti), Springfield, Massachusetts; Department of Rehabilitation Services (Dr Gannotti), University of Hartford, West Hartford, Connecticut; Department of Allied Health Services (Dr Thorpe), University of North Carolina, Chapel Hill, North Carolina; Department of Rehabilitation Sciences (Dr Fuchs), Indiana University-Purdue University, Indianapolis, Indiana.

Purpose. **A systematic review evaluated exercise parameters and ages that produced the most improvement in bone among individuals with cerebral palsy (CP) ages 3 to 21 years.**
Methods. **PubMed, Scopus, Ebscohost, and Web of Science identified potential articles. Covidence was used to identify eligible citations and assess bias. The osteogenic index (OI) was used to evaluate intervention parameters.**
Results. **The database search identified 312 citations. Twelve full-text articles were included. A 1-hour calisthenic exercise program performed 2 to 3 times a week for 8 months targeting each body region had the highest effect size and a substantial OI. Most of the interventions reviewed had low OIs. Activities of longer duration and greater intensity had greater OIs and prepubertal age-enhanced treatment effects.**
Conclusion. **Bone interventions for individuals with CP have low OIs, and principles of mechanostat theory should be applied to exercise dosing. (Pediatr Phys Ther 2022;34:163–170)**
Key words: bone health, cerebral palsy, exercise, mechanostat principles

INTRODUCTION AND PURPOSE

Eight systematic reviews synthesize research about exercise or other interventions for bone health among individuals with cerebral palsy (CP).[1-8] However, it is not clear what type of physical activity or how much is needed to promote bone health among individuals with CP. The American Academy of Cerebral Palsy and Developmental Medicine (AACPDM) CarePathway for the management of osteoporosis among individuals with CP[3] and others[8] indicates that evidence to support the efficacy of weight-bearing activities to promote bone mineral density is unclear. However, it is clear that regardless if individuals with CP walk[4,9] or not,[10,11] there is a risk for poor bone health. The AACPDM CarePathway[3] provides recommendations for surveillance, nutrition, and pharmacologic agents to manage bone health, but it does not provide guidance or education about the optimal dose of exercise for individuals with CP.

0898-5669/110/3402-0163
Pediatric Physical Therapy

Correspondence: Mary E. Gannotti, PT, PhD, University of Hartford, 200 Bloomfield Ave, West Hartford, CT 06117 (gannotti@hartford.edu).

Grant Support: This work was supported by funding from the Academy of Pediatric Physical Therapy.

The authors declare no conflicts of interest.

DOI: 10.1097/PEP.0000000000000878

Physical therapists have not aggressively addressed interventions for bone health for individuals with CP.[12] Consumers and clinicians need to be aware of the critical importance of skeletal health and the high risk for poor bone health among individuals with CP, of all ages, walking or not walking. Bone health should be a priority, and innovations are needed to address poor outcomes in this area.[9,13-16]

Poor skeletal health among adults with CP[17] has consequences for pain, deformity, and function during the lifespan. Findings from public and private administrative claims data demonstrate adults with CP in all age groups have a higher prevalence of osteoporosis than age-matched peers.[18]

Using mechanostat theory and principles[19] when assessing exercise to influence the skeleton among children with CP can provide new insights into effective programs. Mechanostat theory postulates that bone adaptation occurs in response to stresses or strains above a certain threshold.[19] Additionally, bone responds to dynamic loading, not static loading, the loading periods can be short, and the bone needs approximately 4 hours of rest between loading bouts.[19] Bone formation is a process that takes more than 6 months to measure reliably,[20] and greater bone accrual is achieved during prepuberty or times with high growth hormones.[19] Principles of mechanostat theory may be used to guide the design of exercise programs, specifically the osteogenic index (OI).[19] The estimation of bone formation can be calculated using the OI, which is dependent on exercise intensity, number of repetitions, and frequency. Turner and

Robling[21] have identified an equation that predicts bone adaptation to loading (intensity × ln [frequency + 1] × times per week).

Among children developing typically around ages 9 years, Fuchs and Snow[22] used 100 box jumps, 8 times greater than body weight, 3 times a week, for 7 months. Follow-up studies indicated sustainability of treatment effect.[23] This study demonstrated the greatest treatment effect among bone interventions, and the gains were maintained over time.[21,23] Improvement is result of the high-intensity, high-frequency, long-duration exercise and a result of the high level of growth hormones present among the participants in the study. The intervention yielded an estimated OI of 3101.36,[21] and the participants had a mean age of 9 years. Loading during a time of high growth hormones enhances bone accrual.[19] Previous systematic reviews for children with CP have reported on clinical dosing recommendations and synthesized them based on outcomes, not intervention characteristics.[1,2] Bone is most likely underdosed among individuals with CP,[12] and a critical examination of the osteogenic principles of the interventions employed can provide insight.

The primary objective of the systematic objective was to describe the *treatment effectiveness* along with the *osteogenic characteristics* of interventions in published studies. Osteogenic characteristics of interest include: (1) age; (2) type of exercise; (3) ground reaction force; (4) number of repetitions; (5) number of times of day or week; and (6) duration. This framework may advance our understanding of the varying effectiveness of activities based on osteogenic potential and age at time of intervention. The explicit question to be addressed is for individuals with CP ages 3 to 21 years, what are the exercise parameters (type, ground reaction force, number of repetitions, frequency, and duration) and what ages produced the most improvement in bone structure, mass or content, as compared with preintervention or a control group?

METHODS

This systematic review followed Cochrane methodology, a protocol was prepared but not published, and the review is not registered. Treatment effectiveness was defined as changes in bone strength as measured peripheral quantitative computed tomography (pQCT), bone mass or size as measured dual-energy x-ray absorptiometry (DEXA) and reported as either areal bone mineral density in grams per centimeter^2 (aBMD), bone mineral content in grams (BMC), volumetric bone mineral density in grams per centimeter^3 (vBMD), and cortical area in grams per centimeter^2 (CBA). Osteogenic characteristics included identifying the strain/load properties, with low indicating less than body weight (BW) to slightly over 1 time BW, moderate—1.5 times BW to 3 times BW, high—more than 3 times BW. The OI was calculated or estimated for each exercise. If a study reported the ground reaction forces created by the intervention, they were used to calculate the OI. If not, published values of activities were used.[24-26] The OI value of 3101.6 generated by Fuchs et al[27] was used as a benchmark for visual analysis of the selected studies for review.

Searches were performed using the PubMed, Scopus, Ebscohost, and Web of Science databases on January 15, 2020. Key words and phrases in the search included:

1. Cerebral palsy and bone mineral density (BMD)
2. Cerebral palsy and BMD
3. Cerebral palsy and dual x-ray absorptiometry (DXA)
4. Cerebral palsy and DXA
5. Cerebral palsy and DEXA
6. Cerebral palsy and peripheral quantitative computed tomography (pQCT)
7. Cerebral palsy and pQCT
8. Cerebral palsy and skeletal mineralization
9. Cerebral palsy and bone health
10. Cerebral palsy and bone

Several authors were contacted about additional investigations or intervention studies about young people with CP.

Selection Criteria

Studies were included if they met the following criteria:

1. Study design was case study, case control, cohort, or randomized controlled trial (RCT).
2. Included if the intervention group included only individuals with CP ages 3 to 21 years.
3. Included an exercise intervention.
4. Bone strength, mass, or size was an outcome measured using pQCT or DXA.

Studies were excluded if they:

1. Were a narrative review
2. Were a pharmacologic intervention
3. Included no bone outcomes
4. Were published more than 25 years ago
5. Were written in a language other than English

Covidence (https://www.covidence.org/), an online Cochrane technology platform, was used to document the article selection process and generate a PRISMA flowchart. Each article was screened or reviewed by at least 2 authors. Duplicates were removed, and irrelevant articles were removed by examining title, and then, abstract. This was followed by full-text review and selection.

Articles selected were then reviewed independently for content and bias by at least 2 authors. Levels of evidence were assigned using categories from the Oxford Centre for Evidence-Based Medicine.[28] Content extracted included child level of severity (Gross Motor Functional Classification System [GMFCS] level),[29] distribution of impairment, type of activity, duration, frequency, loading of activity, and changes in bone pre- and postintervention. Consensus was obtained among authors on exercise parameters. Cochrane risk of bias[30] was used to rate bias using a 3-point rating scale from low (0), unclear (1), to high (2) in the following areas: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. When conflicts arose, a third reviewer was used to resolve the conflict and achieve consensus. Summary bias scores 0 to 3

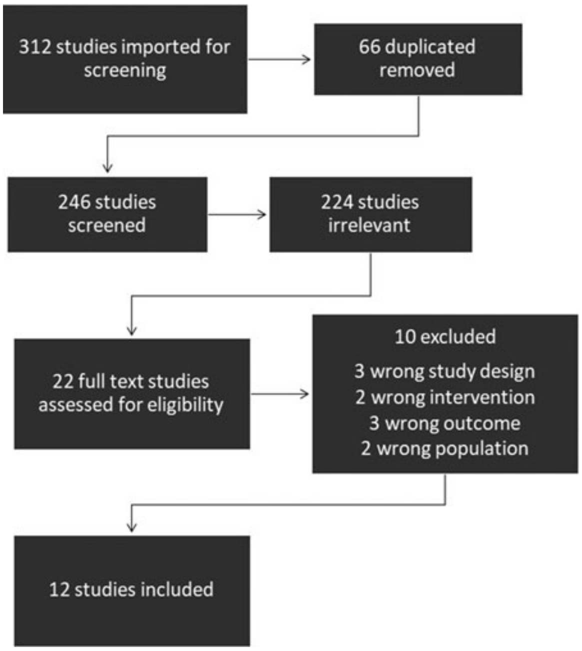

Fig. 1. PRIMSA flowchart.

were considered low, 4 to 6 considered medium, and 7 or more considered high bias.

As the measurement of bone mass, strength, or size can be dependent on equipment, positioning, software, individual deformities, and type of measurements, no comparisons were made among the studies on bone outcome measures directly. The formulas ($d = \frac{Mean1 - Mean2}{SD_{pooled}}$ or $d = \frac{\Delta Mean}{\Delta SD}$)[31] were used to calculate effect size based on study design. When the data were not available, the percent change, or raw change, was calculated. An effect size of 0.2 to 0.3 was considered small, 0.4 to 0.6 moderate, and over 0.6 was considered large.[31,32]

Articles were organized according to level of evidence, risk of bias, and then, treatment effect in the primary data extraction table. Order of articles was maintained in a second table, which identified age range and osteogenic characteristics of activities. The type of activity, strain/loading properties, site specificity, intensity, loading cycles, frequency, and duration were described and the estimated OI was calculated.[21]

RESULTS

The database search identified 312 citations. Duplicates and noneligible types of publications were removed and 246 studies were evaluated on title and abstract. Evaluated studies resulted in 224 studies being excluded and 22 full-text articles assessed for eligibility. After further evaluation by the authors, 10 studies were excluded and 12 full text-articles were included in the quantitative synthesis (Figure 1). Of these 12 studies, 5 randomized control trials, 2 pre-/posttests, and 5 case series and reports were included (Table 1). Two were categorized with low bias, 3 had medium bias, and 7 had high bias (Table 1). No adverse events were reported.

A summary of the 5 RCTs,[33-38] 2 pre-/posttests,[39,40] and 5 case report/case series designs[35,41-44] of weight-bearing activities for individuals with CP is in Tables 1 and 2. The studies included 246 participants, 114 males, across all GMFCS levels with average ages of 9 years, and a range from 4.5 to 21 years. Study design, study bias, child age, means and standard deviations of the pre- and postintervention bone measures for the intervention group, and treatment effect are in Table 2. Table 3 lists the age range, type of activity, osteogenic characteristics, site specificity, intensity, loading cycles, frequency per week, duration, and estimated OI. Types of activities ranged from calisthenics, whole body vibration, weight lifting, cycling, multimodal programs, video games, to dynamic standing programs.

Table 2 identifies large treatment effects in 1 RCT,[33] small treatment effects among 3 studies,[34,36,38] and small to negative percent changes in 1 RCT.[37] One cohort study had negligible effect sizes, while the other demonstrated 2.3% and 5.74% increases in BMD and BMC (Table 2). Among the case studies, there were positive changes.

TABLE 1
Bias of Selected Studies

Cochrane Bias Tool 0 = Low 1 = Unclear 2 = High	Sequence Generation	Allocation Concealment	Blinding Participants and Personnel	Blinding of Assessors	Data Complete	Outcome Reporting	Other Sources	Total	Summary Score
Chad et al[33]	1	0	2	0	0	0	1	5	Medium
Wren et al[38]	0	0	1	0	0	0	1	3	Low
Chen et al[34]	0	0	2	2	2	1	1	8	High
Han et al[36]	0	2	2	1	0	0	1	6	Medium
Ruck et al[37]	0	0	1	1	0	0	1	3	Low
Gusso et al[39]	0	2	2	2	0	0	1	7	High
Stark et al[40]	1	1	2	1	0	0	1	6	Medium
Gannotti et al[44]	2	2	2	1	0	0	1	8	High
Damcott et al[35]	2	2	2	1	0	0	1	8	High
Golomb et al[42]	2	2	2	1	0	0	1	8	High
Golomb et al[41]	2	2	2	2	0	0	1	9	High
Gudjonsdottir and Stemmons Mercer[43]	0	2	2	2	1	0	1	8	High

TABLE 2

Summary of Exercise Interventions to Improve Bone Health in Children With Cerebral Palsy

Author	Study Design	Bias	Mean Age	Bone Measure	Preintervention Intervention Group Mean (SD)	Postintervention Intervention Group Mean (SD)	Treatment Effect Cohen's *d* % Change Raw Change
Chad et al[33]	RCT	Low	9 y	Femoral neck BMC, g Femoral neck aBMD, g/cm^3 Proximal femur BMC, g	1.57 (0.18) 0.36 (0.02) 8.55 (1.32)	1.72 (0.2) 0.38 (0.03) 9.53 (1.43)	$d = 0.878$ $d = 0.83$ $d = 0.794$
Wren et al[38]	RCT	Low	9.4 y	CBA for the tibia midshaft	163 (39)	182 (44)	$d = 0.508$
Chen et al[34]	RCT	Low	6-12 y	aBMD femur, g/cm^2 aBMD lumbar, g/cm^2	0.720 (0.104) 0.578 (0.14)	0.744 (0.097) 0.583 (0.136)	$d = 0.266$ $d = 0.04$
Han et al[36]	RCT	Low	34.43 mo	BMD femur neck	−4.98 (0.68)	−4.8 (1.02)	$d = 0.22$
Ruck et al[37]	RCT	Low	6.2-12.3 y	Lumbar spine aBMD, mg/cm^2 Distal femur R1 aBMD, mg/cm^2 Distal femur R2 aBMD (mg/cm2) Distal femur R3 aBMD, mg/cm^2	Not reported	Not reported	0.013 0.032 −0.002 −0.026
Gusso et al[39]	Pretest, posttest	Low	11.3-20.8 y	DXA, BMD, lower limbs DXA, BMC, lower limbs DXA, BMD, lumbar spine DXA, BMC, femur DXA, BMC, lumbar spine DXA, BMD, femur pQCT, BMD, tibia 50% pQCT, BMD, tibia 20%	1.048 (0.033) 642 (39) 1.095 (0.042) 25.43 (1.45) 51.85 (3.39) 0.954 (0.034) 754 (28) 687 (34)	1.071 (0.033) 655 (38) 1.109 (0.042) 25.68 (1.43) 54.51 (3.33) 0.969 (0.035) 755 (29) 686 (34)	$d = 0.779$ $d = 0.377$ $d = 0.373$ $d = 0.194$ $d = 0.113$ $d = 0.094$ $d = 0.039$ $d = 0.033$
Stark et al[40]	Pretest, posttest	Unclear	9.76 y	BMD BMC	Not reported	Not reported	BMD = 2.3% BMC = 5.74%
Gannotti et al[44]	Case report	High	14-20 y	BMD Lumbar Spine	0.445	0.805	0.360
Damcott et al[35]	Case Series	High	4-9 y	Dynamic standing BMC Dynamic standing BMD Passive standing BMC	Not reported	Not reported	Dynamic loading increased bone
Golomb et al[42]	Case Report	High	15 y	Lower total distal radius BMC Lower ultradistal radius trabecular bone mineral content	40.5% 51.8%	33.50% 37.20%	7% 14.6%
Golomb et al[41]	Case series	High	13-15 y	(1 DXA) Plegic arm aBMD (1 DXA) Plegic arm BMC (1 DXA) Plegic arm B.Ar (2 DXA) Plegic arm aBMD (2 DXA) Plegic arm BMC (2 DXA) Plegic arm B.Ar (3 DXA) Plegic Arm aBMD (3 DXA) Plegic arm BMC (3 DXA) Plegic arm B.Ar (1 pQCT) Plegic arm aBMD (1 pQCT) Plegic Arm BMC (1 pQCT) Plegic arm B.Ar (2 pQCT) Plegic arm aBMD (2 pQCT) Plegic Arm BMC (2 pQCT) Plegic arm B.Ar (3 pQCT) Plegic arm aBMD (3 pQCT) Plegic Arm BMC (3 pQCT) Plegic arm B.Ar	1.00 2.82 8.61 1.83 4.37 8.0 1.878 6.03 11.41 378.3 16.6 43.8 719.1 42.9 59.7 453.8 24.9 54.9	1.02 2.88 8.69 1.59 4.58 8.64 1.66 5.98 11.03 367.8 18.1 49.1 676.9 45.1 66.6 415.7 24.4 58.7	0.02 0.06 0.08 −0.24 0.21 0.64 −0.218 −0.05 −0.38 −10.5 1.5 5.3 −42.2 2.2 6.9 −38.1 −0.5 3.8

(*continues*)

TABLE 2

Summary of Exercise Interventions to Improve Bone Health in Children With Cerebral Palsy (*Continued*)

Author	Study Design	Bias	Mean Age	Bone Measure	Preintervention Intervention Group Mean (SD)	Postintervention Intervention Group Mean (SD)	Treatment Effect Cohen's *d* % Change Raw Change
Gudjonsdottir and Stemmons Mercer[43]	Case series	High	4.5-5.11 y	1 (static, lumbar spine)	0.386	0.406	0.02
				1 (static, right distal	0.266	0.352	0.086
				femur)	0.266	0.449	0.183
				1 (static, left distal femur)	0.473	0.457	−0.016
				2 (static, lumbar spine)	0.313	0.310	−0.003
				2 (static, right proximal	0.377	0.360	−0.017
				femur)	0.385	0.397	0.012
				2 (static, left proximal	0.396	0.395	−0.001
				femur)	0.449	0.434	−0.015
				2 (static, right distal	0.389	0.406	0.017
				femur)	0.403	0.417	0.014
				2 (static, left distal femur)	0.551	0.571	0.02
				3 (dynamic, lumbar spine)	0.539	0.571	0.032
				3 (dynamic, right	0.524	0.550	0.026
				proximal femur)	0.504	0.575	0.071
				3 (dynamic, left proximal	0.433	0.559	0.126
				femur)			
				3 (dynamic, right distal femur)			
				3 (dynamic, left distal femur)			
				4 (dynamic, lumbar spine)			
				4 (dynamic, right distal femur)			
				4 (dynamic, left distal femur)			

Abbreviations: aBMD, areal bone mineral density; B.Ar, bone area; BMC, bone mineral content; BMD, bone mineral density; CBA, cortical bone area; DXA, dual x-ray absorptiometry; pQCT, peripheral quantitative computed tomography; RCT, randomized controlled trial.

Table 3 describes the OI of the interventions, and Figure 2 plots them in order of osteogenic characteristics. Interventions that include weight lifting, calisthenics, cycling, and high-intensity walking and exercise[33,34,40,44] produced the largest OI (Figure 1). Among the RCTs, greatest treatment effect and OI was demonstrated by a 1-hour calisthenics program,[33] 2 to 3 times a week, for 8 months with 20 minutes allotted for each body region (Tables 1 and 2). Daily treatment with a vibrating platform for 6 months[38] had the next highest treatment effect for the tibial midshaft, and had the next highest OI. In both studies, the activity was low to moderately osteogenic, but the frequency was high—3 times a week to daily, and the duration 6 months or more.

Among pre-/posttest studies, a whole body vibration[39] training program 4 times a week for 5 months had the largest effect size, specifically in the tibia. However, increased BMD[40] in the femoral neck and lumbar spine was achieved with a multimodal program several times a week for 6 months with children classified as GMFCS levels II to IV and had the second estimated highest OI of studies reviewed. Case series included dynamic standing devices and mixed martial arts for individuals ranging from GMFCS levels III to V and video games for individuals with hemiplegia. The treatment effect was positive but small. Except for the mixed martial arts exercise, the estimated OIs of the activities were small (Table 3 and Figure 2),

Prepubescent children with a mean age of 9 years demonstrated the largest treatment effects.[33] Of the RCTs, 1 study lasted 8 months,[33] 3 studies lasted a duration of 6 months,[33,36,38] and 1 lasted a duration of 3 months.[34] The 2 pre-/posttest[39,40] designs lasted a duration of 5 and 6 months and the case report/case series[35,41-44] ranged in duration from 2 months to 4 years. Larger effect sizes were seen in interventions that were daily or at least 3 times per week, with a duration of more than 6 months.[33,38]

Activities provided site-specific results. Whole body vibration produced changes in the tibia.[38] Whole body strengthening activities produced changes in the femoral neck.[33] Cycling produced small changes in the distal femur.[34] A multimodal program produced changes in the spine and femoral neck.[40] Calisthenics yielded an estimated OI of 986.19.[33] Mixed martial arts, boxing, and weightlifting yielded an estimated OI of 6574.59 over the duration of the study that lasted 4 years (or 1643.65 per year).[44] Studies with activities that ranked high in osteogenic characteristics and had a higher estimated OI (Table 2 and Figure 2) yielded greater treatment effects. These interventions were multimodal and used multiple muscle groups in the exercise prescription.

TABLE 3

Osteogenic Characteristics of Interventions for Children With Cerebral Palsy Compared to Typical

Author	Age	Type	Strain/Load Properties[a]	Site Specificity	Intensity	Loading Cycles Time	Frequency/ wk	Duration	Estimated Osteogenic Index
Fuchs et al[27]	Typical children prepubescent	Box jumps	High	LSFN	8x BW	100 LC	3x	7 mo	3101.36
Chad et al[33]	Prepubescent	Calisthenics	Low to moderate	LS FN	∼2x BW	∼300 LC 60 min	2-3x	8 mo	986.19
Wren et al[38]	Prepubescent	Vibrating platform	Low to moderate	Tibia	30 Hz at 0.3 g ∼1-1.2x BW	∼300 LC 10 min	7x	6 mo	958.79-1150.55
Chen et al[34]	Prepubescent	Cycling	Low	Distal femur	At 75% 1 RM ∼1-1.2x BW	∼300 LC 40 min	3x	3 mo	205.46-246.55
Han et al[36]	Toddler	Supported standing	Low	LS	∼0.5-1x BW	∼100 LC 2 h	5x	6 mo	276.91-553.81
Ruck et al[37]	Prepubescent	Whole body vibration therapy	Low to moderate	Tibia	12-18 Hz 2.6 g ∼1x BW	∼300 LC 9 min	5x	6 mo	684.85-821.82
Gusso et al[39]	Adolescent	Whole body vibration training	Low to moderate	Tibia	20 Hz 1-mm amplitude ∼1-1.2x BW	∼300 LC 9 min	4x	5 mo	456.57-547.88
Stark et al[40]	Prepubescent	Multimodal training	Moderate	Tibia FN LS	∼2x BW	∼300 LC 40 min	3-7x	6 mo	∼1369.71
Gannotti et al[44]	Adolescent	Mixed martial arts and boxing; weightlifting	Moderate	Spine; upper extremities	∼2x BW	∼300 LC 90 min	2-3x	4 y	∼1643.65/y ∼6574.59 overall
Damcott et al[35]	Young child Prepubescent	Dynamic standing	Low	Femur	∼1.2 BW	∼300 LC 30 min	5x	3 mo	102.73
Golomb et al[42]	Adolescent	Video games	Low	Distal radius	Unclear	21 min	2-3x	14 mo	Unclear
Golomb et al[41]	Adolescent	Video games	Low	Distal radius	Unclear	30 min	5x	3 mo	Unclear
Gudjonsdottir and Stemmons Mercer[43]	Young child	Standing program	Low	LS FN	∼1.2x BW	300 LC 30 min	5x	2 mo	∼273.94

Abbreviations: BW, body weight; FN, femoral neck; LC, loading cycles; LS, lumbar spine; RM, repetition maximum; x, times.
[a]Osteogenic index for each intervention was estimated using estimated ground reaction forces and loading cycles. It was calculated by the following formula: (intensity × ln [frequency + 1] × times per week) × number of week.

DISCUSSION

For individuals with CP ages 3 to 21 years, there are a variety of exercise interventions that have a positive effect on bone mass strength, size, and mass. Exercises with a high ground reaction force or pull/strain on the skeleton, occurred over a long period of time, and occurred prepuberty tended to have a greater treatment effect. Despite differences in physiological development of the bones of individuals with CP and their peers, evidence supports positive response of bone to interventions as described by mechanostat theory.[19] Osteogenic characteristics of bone interventions may have an effect on the treatment effectiveness, and should be considered when designing interventions.

The AACPDM CarePathway for the management of osteoporosis indicates that there is a lack of evidence to support the efficacy of weight-bearing activities to promote bone mineral density. However, based on the studies that were reviewed, there is evidence that weight-bearing activities do promote bone mineral density in individuals with CP.

Interventions with a higher estimated OI were those that included multimodal, compound movements.[33,40,44] Current interventions to improve bone mineral density may be underdosed.

Interventions reviewed did not load the skeleton greater than body weight, and did not use the intensity, frequency, or duration required for osteogenesis. The small sample sizes and varying durations indicate the need for multicenter trials and individuals with similar characteristics that investigate the effect of weight-bearing exercise over a longer period. Standardized interventions, specifically regarding the exercise prescription, assessment, and follow-up measures, are important in the understanding of how to promote bone mineral density.

Participants varied in physical abilities from the ability to walk with no limitations and had hemiplegia to individuals who had difficulty holding their heads up. Participants with more severe gross motor impairment were involved in standing programs, interventions with the lowest OI. More creative and innovative movement programs should be designed for individuals classified GMFCS level V to promote skeletal health and prevent

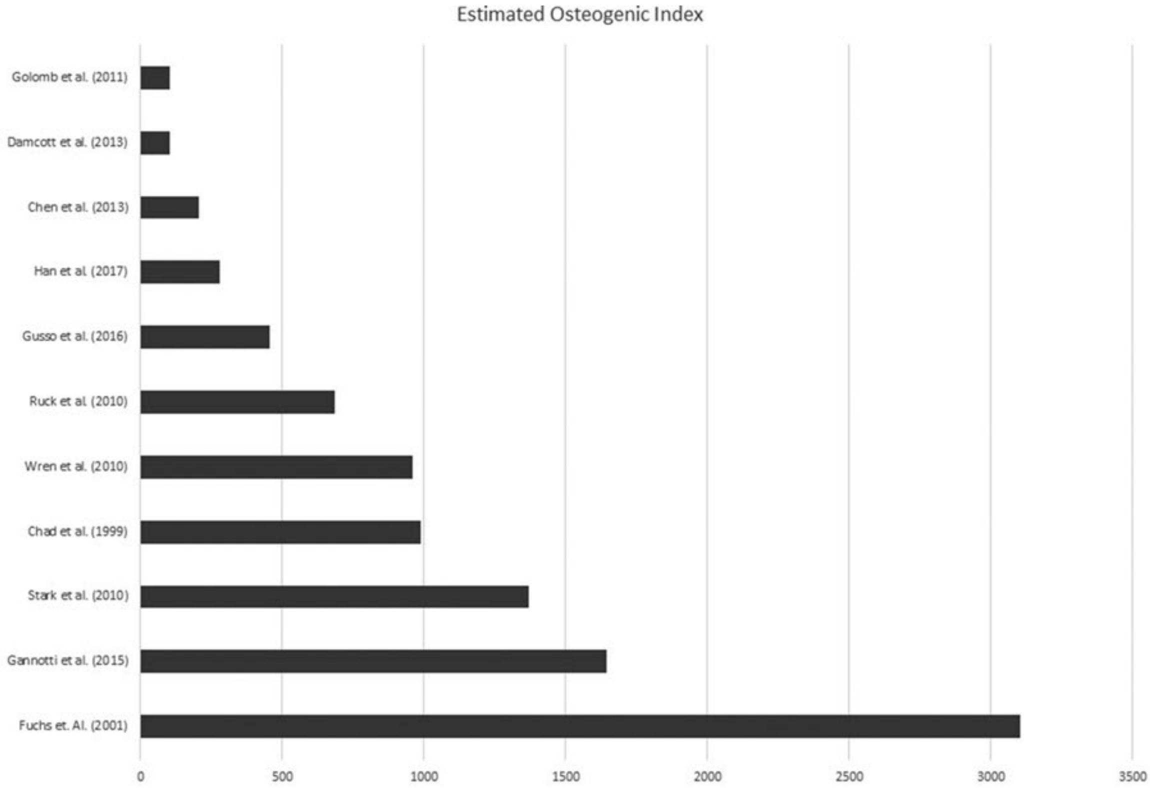

Fig. 2. Osteogenic index estimates for interventions.

secondary conditions. Individuals classified GMFCS level IV did participate in intense, high-frequency programs.[40,44]

There is risk of bias across studies, as many of the studies did not control for other factors highly related to bone health such as genetics, nutrition, and growth hormone levels. There was 1 crossover design to test the bone changes with and without the intervention in a group of children, but this did not control for some factors. There are a myriad of issues around measuring bone using either pQCT or DXA, including differences in software, hardware, technician, and interpretation.[20] The OI was estimated for studies with no published ground reaction forces or unclear for the upper extremities. The sample sizes are small, and the characteristics of the participants heterogenous. This limits the ability to pool the findings and generalize.

Recommendations for clinicians and researchers include designing and using interventions that incorporate principles of mechanostat theory and use OI for activities. Individuals with CP regardless of their ability to walk have a propensity for poor bone health. Small bouts of more than usual loading with novel multidirectional forces are warranted for all individuals with CP across the lifespan, but particularly in prepuberty. Continued creativity and innovation are needed for those who cannot move voluntarily, for both the design of activities and the measurement of outcomes.

CONCLUSION

Bone interventions for individuals with CP have low OI, and principles of mechanostat theory should be applied to exercise dosing. Exercise with higher OI demonstrated increased treatment effect on bone health among individuals with CP 3 years to 21 years of age. Principles of mechanostat theory[19] should be applied to interventions to improve bone health among individuals with CP. Use of these concepts may aid in improvement of treatment effectiveness among bone health interventions.

REFERENCES

1. Hough JP, Boyd RN, Keating JL. Systematic review of interventions for low bone mineral density in children with cerebral palsy. *Pediatrics.* 2010;125(3):e670-e678.
2. Paleg GS, Smith BA, Glickman LB. Systematic review and evidence-based clinical recommendations for dosing of pediatric supported standing programs. *Pediatr Phys Ther.* 2013;25(3):232-247.
3. Fehlings D, Switzer L, Agarwal P, et al. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: a systematic review. *Dev Med Child Neurol.* 2012;54(2):106-116.
4. Mus-Peters CTR, Huisstede BMA, Noten S, Hitters M, van der Slot WMA, van den Berg-Emons RJG. Low bone mineral density in walking persons with cerebral palsy? A systematic review. *Disabil Rehabil.* 2019;41(20):2392-2402.
5. Ozel S, Switzer L, Macintosh A, Fehlings D. Informing evidence-based clinical practice guidelines for children with cerebral palsy at risk of osteoporosis: an update. *Dev Med Child Neurol.* 2016;58(9):918-923.
6. Pin TW. Effectiveness of static weight-bearing exercises in children with cerebral palsy. *Pediatr Phys Ther.* 2007;19(1):62-73.
7. Saquetto M, Carvalho V, Silva C, Conceicao C, Gomes-Neto M. The effects of whole body vibration on mobility and balance in children with cerebral palsy: a systematic review with meta-analysis. *J Musculoskelet Neuronal Interact.* 2015;15(2):137-144.
8. Novak I, Morgan C, Fahey M, et al. State of the Evidence Traffic Lights 2019: systematic review of interventions for preventing and treating children with cerebral palsy. *Curr Neurol Neurosci Rep.* 2020;20(2):3.

9. Whitney DG, Peterson MD, Devlin MJ, Caird MS, Hurvitz EA, Modlesky CM. Bone marrow fat physiology in relation to skeletal metabolism and cardiometabolic disease risk in children with cerebral palsy. *Am J Phys Med Rehabil*. 2018;97(12):911-919.
10. Mergler S, Evenhuis HM, Boot AM, et al. Epidemiology of low bone mineral density and fractures in children with severe cerebral palsy: a systematic review. *Dev Med Child Neurol*. 2009;51(10):773-778.
11. Stevenson RD, Conaway M, Barrington JW, Cuthill SL, Worley G, Henderson RC. Fracture rate in children with cerebral palsy. *Pediatr Rehabil*. 2006;9(4):396-403.
12. Gannotti ME, Liquori BM, Thorpe DE, Fuchs RK. Designing exercise to improve bone health among individuals with cerebral palsy. *Pediatr Phys Ther*. 2021;33(1):50-56.
13. Whitney DG. Racial differences in skeletal fragility but not osteoarthritis among women and men with cerebral palsy. *Bone Rep*. 2019;11:100219.
14. Whitney DG, Alford AI, Devlin MJ, Caird MS, Hurvitz EA, Peterson MD. Adults with cerebral palsy have higher prevalence of fracture compared with adults without cerebral palsy independent of osteoporosis and cardiometabolic diseases. *J Bone Miner Res*. 2019;34(7):1240-1247.
15. Whitney DG, Singh H, Miller F, et al. Cortical bone deficit and fat infiltration of bone marrow and skeletal muscle in walking children with mild spastic cerebral palsy. *Bone*. 2017;94:90-97.
16. Whitney DG, Whitney RT, Prisby RD, Jepsen KJ. Low-trauma fracture increases 12-month incidence of cardiovascular disease for adults with cerebral palsy. *J Orthop Res*. 2020;38(4):803-810.
17. Sheridan KJ. Osteoporosis in adults with cerebral palsy. *Dev Med Child Neurol*. 2009;51(suppl 4):38-51.
18. French ZP, Caird MS, Whitney DG. Osteoporosis epidemiology among adults with cerebral palsy: findings from private and public administrative claims data. *JBMR Plus*. 2019;3(11):e10231.
19. Robling AG, Fuchs RK, Burr D. Mechanical adaptation In: Burr D, Allen M, eds. *Basic and Applied Bone Biology*. San Diego, CA: Elsevier; 2014: 175-203.
20. Specker BL, Schoenau E. Quantitative bone analysis in children: current methods and recommendations. *J Pediatr*. 2005;146(6):726-731.
21. Turner CH, Robling AG. Designing exercise regimens to increase bone strength. *Exerc Sport Sci Rev*. 2003;31(1):45-50.
22. Fuchs RK, Snow CM. Gains in hip bone mass from high-impact training are maintained: a randomized controlled trial in children. *J Pediatr*. 2002;141(3):357-362.
23. Gunter K, Baxter-Jones AD, Mirwald RL, et al. Impact exercise increases BMC during growth: an 8-year longitudinal study. *J Bone Miner Res*. 2008;23(7):986-993.
24. Santos-Rocha R, Veloso A, Machado ML. Analysis of ground reaction forces in step exercise depending on step pattern and stepping rate. *J Strength Cond Res*. 2009;23(1):209-224.
25. Nilsson J, Thorstensson A. Ground reaction forces at different speeds of human walking and running. *Acta Physiol Scand*. 1989;136(2): 217-227.
26. Bergmann G, Kutzner I, Bender A, et al. Loading of the hip and knee joints during whole body vibration training. *PLoS One*. 2018;13(12): e0207014.
27. Fuchs RK, Bauer JJ, Snow CM. Jumping improves hip and lumbar spine bone mass in prepubescent children: a randomized controlled trial. *J Bone Miner Res*. 2001;16(1):148-156.
28. OCEBM Levels of Evidence Working Group. *The Oxford 2011 Levels of Evidence*. London, England: Oxford Centre for Evidence-Based Medicine; 2001.
29. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol*. 1997;39(4): 214-223.
30. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343: d5928.
31. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. New York: NY: Routledge Academic; 1988.
32. Sullivan GM, Feinn R. Using effect size—or why the P value is not enough. *J Grad Med Educ*. 2012;4(3):279-282.
33. Chad KE, Bailey DA, McKay HA, Zello GA, Snyder RE. The effect of a weight-bearing physical activity program on bone mineral content and estimated volumetric density in children with spastic cerebral palsy. *J Pediatr*. 1999;135(1):115-117.
34. Chen CL, Chen CY, Liaw MY, Chung CY, Wang CJ, Hong WH. Efficacy of home-based virtual cycling training on bone mineral density in walking children with cerebral palsy. *Osteoporos Int*. 2013;24(4):1399-1406.
35. Damcott M, Blochlinger S, Foulds R. Effects of passive versus dynamic loading interventions on bone health in children who are nonwalking. *Pediatr Phys Ther*. 2013;25(3):248-255.
36. Han EY, Choi JH, Kim SH, Im SH. The effect of weight bearing on bone mineral density and bone growth in children with cerebral palsy: a randomized controlled preliminary trial. *Medicine (Baltimore)*. 2017; 96(10):e5896.
37. Ruck J, Chabot G, Rauch F. Vibration treatment in cerebral palsy: a randomized controlled pilot study. *J Musculoskelet Neuronal Interact*. 2010; 10(1):77-83.
38. Wren TA, Lee DC, Hara R, et al. Effect of high-frequency, low-magnitude vibration on bone and muscle in children with cerebral palsy. *J Pediatr Orthop*. 2010;30(7):732-738.
39. Gusso S, Munns CF, Colle P, et al. Effects of whole-body vibration training on physical function, bone and muscle mass in adolescents and young adults with cerebral palsy. *Sci Rep*. 2016;6:22518.
40. Stark C, Nikopoulou-Smyrni P, Stabrey A, Semler O, Schoenau E. Effect of a new physiotherapy concept on bone mineral density, muscle force and gross motor function in children with bilateral cerebral palsy. *J Musculoskelet Neuronal Interact*. 2010;10(2):151-158.
41. Golomb MR, McDonald BC, Warden SJ, et al. In-home virtual reality videogame telerehabilitation in adolescents with hemiplegic cerebral palsy. *Arch Phys Med Rehabil*. 2010;91(1):1-8.e1.
42. Golomb MR, Warden SJ, Fess E, et al. Maintained hand function and forearm bone health 14 months after an in-home virtual-reality videogame hand telerehabilitation intervention in an adolescent with hemiplegic cerebral palsy. *J Child Neurol*. 2011;26(3):389-393.
43. Gudjonsdottir B, Stemmons Mercer V. Effects of a dynamic versus a static prone stander on bone mineral density and behavior in 4 children with severe cerebral palsy. *Pediatr Phys Ther*. 2002;14(1):38-46.
44. Gannotti ME, Fuchs RK, Roberts DE, Hobbs N, Cannon IM. Health benefits of seated speed, resistance, and power training for an individual with spastic quadriplegic cerebral palsy: a case report. *J Pediatr Rehabil Med*. 2015;8(3):251-257.