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REVIEW ARTICLE

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Physical exercise in the prevention and rehabilitation of Osteopenia in premature infants and children with Down Syndrome: a systematic review

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ABSTRACT

Introduction: Osteopenia is a systemic metabolic disease derived from decreased bone formation and/or increased resorption without compromising microarchitecture, causing increased fragility and susceptibility to fractures, which can affect growth in childhood and adolescence. **Objective:** Identify which interventions through physical exercise can help in the treatment and prevention of osteopenia/osteoporosis in premature infants and children with Down Syndrome. **Methods:** The searches were conducted in specific databases in Health Sciences, structured in the form PICOS, including randomized clinical trials related to physical exercise against osteopenia in premature children and with Down Syndrome from 0 to 12, using the Health Sciences Descriptors to identify the keywords. Studies with high methodological quality were eligible for meta-analysis in the random effects model. **Results:** Of the 15 articles analyzed, it was observed that both infants, children, and adolescents in the experimental groups, who performed physical exercise, showed statistically significant differences in at least one of the biomarkers of bone formation or bone resorption and, in the same way, showed statistical differences in densitometry and ultrasound measurements. The meta-analysis performed with the studies in preterm infants showed statistically significant mean differences of 0.77 and 0.61 for bone formation in the intervention group and 1.07 for the intensity of 10 repetitions in the Moyer and Mileur protocol. **Conclusion:** Physical exercise contributes to greater bone formation and reduction of bone resorption, effectively treating and preventing metabolic diseases of osteo in premature infants and children with Down Syndrome.

Keywords: Physiotherapy; Exercise; Osteometabolic diseases; Bone formation; Prematurity; Pediatrics.

INTRODUCTION

Osteopenia is a systemic metabolic disease due to decreased bone formation and/or increased resorption without compromising microarchitecture, causing increased fragility and susceptibility to fractures[1-3]. During childhood, remodeling can be altered by intrinsic factors; and extrinsic factors[3]. These risk factors need to be investigated, as osteopenia in childhood is usually asymptomatic, however, its implications have as main signs the impairment of general growth, inadequate muscle development, bone malformation, and the occurrence of fractures after light trauma, being a precursor of osteoporosis[1,4-6].

Preterm infants have some intrinsic and extrinsic risk factors, such as limited intrauterine bone mass accumulation, deficiency in the intake of the main substrates for extrauterine bone formation (calcium and phosphorus), prolonged immobilization, use of total parenteral nutrition and drugs that increase the loss of calcium[3]. In addition, the last trimester of pregnancy is where the greatest accumulation of minerals occurs, where the mother transfers them in greater amounts to the fetus, and it is extremely difficult to match this accumulation in the extrauterine environment bone[2]. Regarding Down Syndrome, among the physical changes we can mention thyroid dysfunction, delay in gross motor development, hypotonia, and low muscle strength, which can contribute to a low composition of bone mineral density in these individuals, favoring the development of osteopenia in the childhood and adult osteoporosis, in addition to failure to eat dairy products, vitamin D and physical inactivity, which also impact bone tissue[7].

It is common to find prevention and treatment strategies for osteometabolic diseases in literature, including calcium and phosphorus supplementation; on the other hand, it is more difficult to identify studies that only address the interference of physical exercise on bone formation. However, we have studies that suggest the help of exercise in promoting bone mineral density and provide evidence that regular physical activity promotes an increase in bone content[8]. Physical exercise can favor bone development through indirect effects, with the

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action of hormones and growth factors, and direct effects caused by mechanical forces[9]. This application of forces causes a greater osteogenic stimulus on the bone tissue since the mechanical stress favors structural changes called bone remodeling[10]. These mechanical actions generate differences in electrical potentials, which stimulate cellular activity leading to the deposition of minerals at stress points. This is all explained by the piezoelectric effect that is characterized by loads of negative effects at the site of action increased bone formation by stimulating local growth factors and favoring bone strengthening in the stimulated region[9-11]. Given that interventions through physical exercise are used to promote bone formation and mineralization, they need to be analyzed to provide professionals with statistically and clinically significant data on their effectiveness.

Bearing in mind that osteopenia is a contributor to complications such as rickets and fractures, and can affect growth in childhood and adolescence[3,12], it is necessary to know more about exercise treatment in these situations, so that it is possible to develop an adequate and individualized intervention.

The objective of this research was to identify which interventions through physical exercise can help in the treatment and prevention of osteopenia in premature infants and children with Down Syndrome.

METHODS

Intervention studies were included in this review, especially randomized clinical trials related to physiotherapeutic treatment for osteopenia in premature children and those with Down Syndrome aged 0 to 12 years for bone development and formation, excluding those who did not use physical exercises or physical therapy techniques. As for the outcome measure, we included those that considered bone mineralization, bone formation, and bone resorption. The studies should have been published between 2011 and February 2021, without delimitation of

the place of publication and languages, all were translated when necessary and possible. Studies with unclear, poorly described, or inappropriate interventions, literature reviews, meta-analysis studies, cross-sectional studies, and letters to the editor, in addition to those published only in abstract form, were considered ineligible.

The following specific bibliographic databases in Health Sciences were consulted: PubMed, PEDro, Medline, Embase, Cochrane, and Lilacs. The platform used to access these databases was the Capes Journal Portal through remote access through the Federated Academic Community (CAFe). Lists of references cited in systematic reviews on related topics were manually examined[2,4,8,13].

Two examiners performed the eligibility process independently and blindly, and disagreements were resolved by consensus. Once the searches were completed, duplicate references were eliminated; then, based on the titles and later the abstracts, only potentially eligible studies were selected for full evaluation.

Search strategies

The Health Sciences Descriptors DeCS were used to identify and refine the keywords, and the search was structured in the form PICOS, an acronym for population, intervention, comparison, outcomes, and study. For P (target population) we defined “osteopenia”, “syndromes”, “preterm infants” and “pediatrics” (osteopenia; metabolic bone disease; syndrome; preterm infants; pediatrics); for I (intervention) we used “physical exercise”, “physiotherapy” and “rehabilitation” (physical therapy, physiotherapy, exercise, rehabilitation); we don't use C (control); for O (outcome) we apply “bone mineral density” and “bone formation”; and for S (types of study) we prioritized “randomized clinical trials”. Similar terms were combined using the “OR” operator, and for descriptors that were added the “AND”

operator was used. The filters used to refine the searches were the study design and year of publication (last 10 years), as provided for in the inclusion criteria.

The evaluation of the methodological quality of the articles included in the study was conducted using the PEDro scale, indicating the score obtained from 0 to 10 points, which considers an article of excellent quality as of grade 7. This scale evaluates: the randomization of subjects, secret allocation, homogeneous baseline characteristics, blinding of all subjects, blinding of therapists, blinding of raters, key outcome measures measured in more than 85% of the population, analysis by intention to treat, statistical comparisons between groups and presentation of measures of precision and variability.

A clinical data extraction form was prepared by the researchers based on the Methodological Guidelines of the Brazilian Ministry of Health[14]. Therefore, for each trial included, the following information was collected: type of study and year of publication; methodological characteristics, such as blinding scheme, and follow-up time; characteristics of the trial population, along with specific inclusion and exclusion criteria; number of participants in each group and number of losses per arm; description of the intervention, duration, frequency and type in the control (CG) and experimental group (EG); investigated outcomes with their respective diagnostic criteria and measurement units; results obtained for each outcome.

After selection and reading, the tests were qualified in terms of methodology through the PEDro scale[15]. Cochrane ROB-2 scale[16] was used to determine the risk of bias for each study (Figure 1); Review Manager (RevMan) version 5.4.1 desktop software, developed by Cochrane, was used to assist in the analysis.

Statistical analysis was performed using RevMan 5.4.1 software. The results sought were of the continuous type, since the measurements could take any integer or fractional values, and were analyzed using the weighted mean difference, since the measurement units were not the same for all studies, and a confidence interval of 95% was reported for all estimates.

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Eligibility of studies for meta-analysis

Studies with high methodological quality were considered eligible, therefore with a PEDro score ≥7 points, and a lower risk of bias. In addition, studies that did not have the necessary data were not included. We used the Forest Plot chart to structure the data, and a table organized in alphabetical order, which had the number of participants per group for each study (N), standard deviation, and mean, in addition to the individual weight of each study, individual weighted average and general, measures of heterogeneity and general effect.

We used meta-analysis in the random effects model, as the studies differed in their methodology, and the weight of the studies was calculated using inverse variance, that is, the greater the variability, the lower the participation of the study in the conclusion. We examined the heterogeneity between the assays, inspecting the Forest Plot and the heterogeneity quantifier I^2.

RESULTS

Of the 123 articles initially selected, 19 studies were included, and of these, after further review, 04 were excluded for being outside the publication date criteria, not targeting children as the audience, and being reviews, resulting in a final sample of 15 studies.

All studies were randomized controlled trials that included a control group and an intervention group, except for three, which had two or more intervention groups. Most had a high-quality grade based on the PEDro scale. Studies on premature infants started interventions from 26 weeks of gestational age, and those that approached children with Down Syndrome, from 7 years of age (Table 1).

The total population analyzed in all studies was 481 individuals, of which 225 belong to the exercise group (EG) and 208 belong to the control group (CG). To count the number of

individuals in the EG and CG, the study by Reza et al.[17] did not present the specific number of participants who were distributed by groups, identifying only the total number of individuals.

Regarding studies with preterm infants, in 2 of the trials, Litmanovitz et al.[18] and Moyer-Mileur et al.[19] included two experimental groups. Across the studies, at baseline, no differences between sex, gestational age, weight, or height, or at baseline values of key outcome measures. Gestational age ranged from 26 to 36 weeks; birth weight, from 900 g to 1,900 g; and height, from 30cm to 43cm.

In all studies, babies were considered stable according to inclusion criteria established by the authors as an inclusion criterion, the authors considered that the babies were clinically stable. Ten studies specified that the babies received complete enteral nutrition, and five specified a similar nutritional contribution among all participants since the form of ingestion and the calories consumed per day were similar. Likewise, all studies required participants to have no health complications.

About the Down Syndrome population, there were also no statistical differences between age, sex, weight, or height at baseline, or in the initial measures of primary outcome. The children's ages ranged from 7 to 19 years; their weight, from 40.1 kg to 49.3 kg; and height, from 141.9 cm to 148.8 cm. Noting that the study Matute-Llorente et al.[20] compared a group of SD children with that of typical children. Regarding diet and exercise, in all studies, it was recommended that they stick with what they were before the intervention. In the same way as the studies in preterm infants, these required that the participants had no health complications.

Characteristics of interventions

Regarding the studies on preterm infants, 9 based the interventions on the Moyer-Mileur protocol, in which some modified time and frequency, two performed passive movements of flexion and extension associated with the movement of compression in the joints (among these,

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one added massage in the whole body of the premature baby). Among the studies involving children with Down Syndrome, the interventions were different among all. The study that observed the effect of physical exercise in these children for 21 weeks conducted an intervention based on an activity circuit that included jumping, wall push-ups, gymnastics with elastic bands (containing resistance), and exercises with medicine balls. Already in what had in its intervention the implementation of calcium introduced in cow's milk, weightlifting exercises were performed. Finally, in the study involving the vibrating platform, the participants exercised while standing on it, and one of the exercises mentioned was the squat.

Of all the studies analyzed by this review, 9 used biochemical markers as an outcome measure; 7, ultrasound (US); 5, bone mineral densitometry (BMD) or dual-energy X-ray absorptiometry (DXA); and 9 compared anthropometric measurements, such as weight and height. The biochemical markers of bone formation observed in the assays were: stereospecific alkaline phosphatase (BSAP/BAP); carboxyterminal procollagen type I peptide (PICP); parathyroid hormone (PTH); alkaline phosphatase (ALP); insulin growth factor type I (IGF-1); mid-fragment of urinary osteocalcin (U-mid OC). The resorption markers were: carboxyterminal telopeptide of collagen type I (ICTP); pyridoxine (Pyd); deoxypyridinoline (DPD); Calcium (Ca). The improvement in bone formation and quality was determined by the increase in formation markers and reduction in resorption markers.

Regarding the use of ultrasound or DXA, of the 12 studies that used them as a measure of bone formation, only Shaw et al.[21] found no significant differences between the exercise group and the control group regarding bone development. The study by Matute-Llorente et al.[20] reported that the group with typical children had better results compared to the group with DS children, but all other studies that addressed premature infants – Erdem et al.[12], Chen et al.[22], Tosun et al.[23], Litmanovitz et al.[18], Haley et al.[24], Sezer et al.[25], Moyer-Mileur et al.[19], Vignochi et al.[26], González-Agüero et al.[27] and Reza et al.[17] also found statistically significant post-

intervention differences in bone formation measurement. Infants, children, and adolescents belonging to the physical exercise group showed statistically significant differences in 6 of the 7 studies with ultrasound (85.71%) and in all 5 performed with bone densitometry (100%).

In trials that used biochemical markers of bone formation, 3 found differences in BSAP[26,28,29], 2 found differences in favor of the intervention group in measures of PICP[19,30,] and none identified differences in ALP. Regarding bone resorption biomarkers, a significant reduction in DPD was found[29]; only Aly et al.[30] reported a favorable difference to the intervention group in calcium measurements, and only two studies found no differences in any marker[19,21]. Infants in the experimental groups showed statistically significant differences in at least one of the bone formation biomarkers in 6 of 8 studies (75%) and in 4 of 7 studies (57.14%) with bone resorption markers.

Regarding anthropometric measurements, of the 5 studies that compared head circumference, none found differences between the groups; only 3 of 9 (33.33%) trials that compared reported differences in weight measures in favor of the intervention group (Table 2).

Meta-analysis

For all the outcomes and graphs presented, the included studies presented a comparison between the control group and only one intervention group. All reported some type of concern about the risks of bias, and the greatest concerns were found in the blinding schemes; however, all had a PEDro score above 7 (Figure 2).

Statistically significant differences were found, with a total mean difference of 0.77 (ranging from 0.47 to 1.08), and the studies by Sezer et al.[25] (n=24) and Tosun et al.[23] (n=40) found the greatest differences, respectively 1.14 and 1.49, with a confidence interval of 95%, favorable to the intervention group (Figure 3).

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Regarding bone formation markers, the total mean difference was 0.61, ranging between 0.11 and 1.10, with a confidence interval of 95%, favorable to the intervention group. The studies that found the greatest difference were those by Vignochi et al.[26] (n=30) and Nemet et al.[28] (n=24), respectively 0.91 and 1.74 (Figure 4).

Comparing the point of greatest divergence – the intensity of the exercises – in the protocol by Moyer-Mileur et al.[19], which was the most used among preterm studies, we found that, above 5 repetitions, statistically significant differences are observed. With only 5 repetitions, the mean difference found was 0.78, with a confidence interval of 95%, with no significant differences being reported, with a heterogeneity of 66% (I^2). The studies that used more than 5 repetitions showed a mean difference of 1.07 and 0.72, respectively, for 10 repetitions and 5 to 8 repetitions, with a confidence interval of 95% and heterogeneity of 0% (I^2). In general, studies that used the Moyer-Mileur et al.[19] had statistically relevant findings, with a mean difference of 0.80, ranging between 0.54 and 1.05, with a confidence interval of 95% and heterogeneity of 11% (I^2).

DISCUSSION

Most of the studies with preterm infants used passive mobilization with joint compression presented by Moyer-Mileur, however, they distinguished as to the intensity and frequency of the intervention, period of application, control group, and professional who performed the therapy. The administration of a placebo in the CG could be useful to eliminate bias and effects arising from any other interaction since these babies spent a lot of time in the incubator. Regarding frequency and intensity, according to some results, it was observed that the greater the variables, the better the effects were found. Regarding treatment time, studies conducted up to hospital discharge and up to 44 weeks found similar effects.

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The only difference is that of Shaw et al.[21] where the treatment time lasted until the preterm infants completed 40 weeks of gestational age, however, the result did not show any difference in the measurement units between the EG and CG groups. Interventions in the DS population were quite varied when compared with interventions in PT, the studies by Gonzalez-Aguero et al.[27] and Reza et al.[17] with different physical exercise protocols and impact exercises, while Matute-Llorente et al.[20] used a vibrating platform. This divergence in the frequency, type, and intensity of exercises, that is, protocols without standardization, makes it difficult to replicate and reliably determine which exercises are more suitable for the treatment of children with DS and osteopenia. As for the protocol used, Moyer-Mileur et al.[19] in most of the articles, it is questionable whether there are no other techniques to be applied and studied, leaving the suggestion for future studies to expand the treatments within the scope of physiotherapy and follow the PT after hospital discharge on an outpatient basis, focused on osteometabolic diseases.

Regarding the time of initiation of interventions, the discrepancy that occurs between populations is notorious, since in PT the interventions started while still in the hospital, while for children with DS, the onset was late, starting at 7 years of age, suggesting that future studies apply interventions earlier in these children, as this may have an impact on the results obtained. On the other hand, the time of the effect of the treatments was carried out in the short term, and, in the scientific area, the importance of studies with longer follow-up time to prove cause and effect is common, thus demanding future studies that monitor long-term results to see how long the treatment effects last.

However, another significant difference observed was that the health professionals responsible for implementing the intervention varied from study to study. In the study by Shaw et al.[21,] it was identified that the physical therapist taught the intervention process to another health professional and those responsible for the children. The protocol used by the authors may

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be fragile since it is possible that the intervention participants did not understand clearly or did not perform at the established frequency. The protocol did not include the number of repetitions, the main researcher and five nurses were trained by a qualified physical therapist, and then the researcher passed the training on to the mothers who started to apply the exercise after a week of intervention by the specialists, under the supervision of these specialists. After discharge, they continued at home receiving standardized videos of the exercises and were asked to make a daily record of the intervention on a sheet provided by the professionals.

Although a substantial portion of the studies analyzed are similar but have different assessment measures, it is still possible to emphasize that, regardless of the meaning used, physical exercise has an impact on bone quality. Chen et al.[22] and Litmanovitz et al.[18] were the only studies that evaluated at the beginning, in the middle, and at the end of the interventions, making it possible to know when the changes occurred, while the other authors carried out the evaluation only at the beginning and at the end of the interventions, not identifying, thus, the period of changes, bringing the indication of the evaluation during the protocol application.

Overall, most studies reported that interventions increased bone content through improvements in bone densitometry, increased biochemical markers of bone formation, and reduced markers of bone resorption. It is known that DXA is the gold standard for bone assessment, however, we cannot discard the findings regarding biomarkers, which also showed statistically significant results favorable to the intervention group.

Except for Nemet et al.[28], Shawn et al.[21], Moyer-Mileur et al.[19,] and Vignochi et al.[26], who found differences in the weight of post-intervention participants favorable to the EG, no other study reported these differences. Therefore, the exercise with the objective of bone formation does not interfere with the anthropometric measurements, and the opposite does not happen either.

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The studies differ in methodological, however, it is observed that trials with better methodology and lower bias resemble others of lower quality in terms of results, that is, regardless of quality, they all reached the same conclusion that the exercise physical activity contributes to bone formation. It is important to emphasize that more than half of the studies on DS had low methodological quality, obtaining a score of 5 on the PEDro scale, highlighting that they did not perform a blinding scheme in any parameter and did not report how the subjects were allocated, which is therefore inadequate. Regarding the PT studies, all of them lost points in terms of the therapist "blinding", but this is explained by the nature of the intervention, except Nemet et al.[28] and Chen et al.[22], who did not "blind" the evaluators, all the others did; regarding the "blinding" of the patient, all met this requirement, given the study population.

Except for Haley et al.[24], Sezer et al.[25], Moyer-Mileur et al.[19], Vignochi et al.[26,] and González-Agüero et al.[27], who did not report or did not perform an intention-to-treat analysis, all presented this item, which is an important bias control. The studies by Vignochi et al.[29], Aly et al.[30], Gonzáles-Agüero et al.[27,] and Reza et al.[17] did not report what was done with the control group, which impairs the control of bias since the GC favors the discarding of the influence of other factors in the experiment. In addition to being important in terms of bias, the lack of inadequacy of these factors makes it difficult to replicate the protocol in clinical practice, since there is no consensus between them. The use of the PEDro scale and the ROB-2 scale made it possible for this review to find extremely valuable information on the methodological quality and risks of bias in the analyzed articles.

Limitations of the study We identified the inclusion criterion was established with a publication date within the last 10 years, however, during the searches, we observed a lack of high-quality studies on the topic within this time, necessitating an extension. Another crucial point would be to include studies or information not only about exercise but also about the influence of growth during this process on osteopenia.

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Conclusion

The information obtained in the present review suggests that the Moyer-Mileur is the best intervention for osteopenia in premature infants, however the same was not observed for Down Syndrome because there was no standardization of protocols in the analyzed studies.

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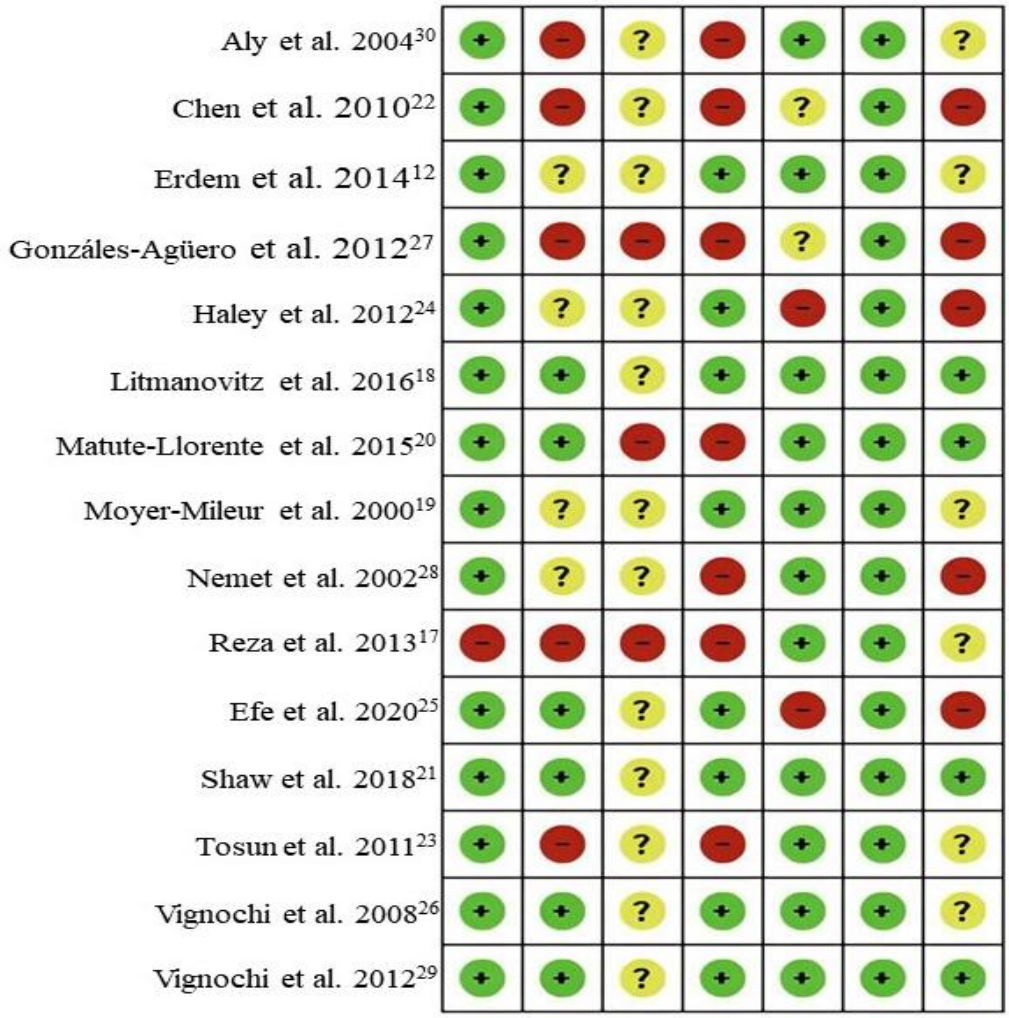
Figure 1: Bias for each study



Green: minimal risk of bias; yellow: some doubts; red: elevated risk of bias.

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Table 1: List of participant characteristics and methodology of each study

	Characteristics of the Participants					Study Characteristics	
	N			Details			
Studies	**EG**	**GC**	**Age**	**Population**	**Design of the study**	**PEDro**	**ROB-2**
Vignochi et al. 2012[29]	15	15	NM	Premature ≤ 35GA	RCT	8/10	some concerns
Aly et al. 2004[30]	15	15	2 weeks	Premature ≤ 35GA	RCT	8/10	some concerns
Nemet et al. 2002[28]	12	12	NM	Premature	RCT	7/10	some concerns
Shaw et al. 2018[21]	26	24	NM	Premature	RCT	8/10	some concerns
Erdem et al. 2015[12]	14	14	≤3days	Premature 26 to 36GA	RCT	8/10	some concerns
Chen et al. 2010[22]	8	8	1 week	Premature	RCT	7/10	some concerns
Tosun et al. 2011[23]	20	20	≤3days	Premature 26 to 36GA	RCT	8/10	some concerns
Litmanovitz et al. 2016[18]	12EG1 13EG2	11	≤2 days	Premature	RCT	8/10	some concerns
Haley et al. 2012[24]	20	20	NM	Premature 29 to 36GA	RCT	7/10	some concerns
Efe et al. 2020[25]	12	12	NM	Premature 28 to 32GA	RCT	7/10	some concerns
Moyer-Mileur et al. 2000[19]	16	16	NM	Premature 26 to 32GA	RCT	7/10	some concerns
Vignochi et al. 2008[26]	15	14	NM	Premature 26 to 34GA	RCT	8/10	some concerns
González-Agüero et al. 2012[27]	14	14	10 to 19	Down syndrome	RCT	8/10	some concerns
Reza et al. 2013[17]	NM	NM	7 to 12	Down syndrome	RCT	5/10	Many concerns
Matute-Llorente et al. 2016[20]	13	13	12 to 18	Down syndrome	RCT	5/10	Many concerns

GA: gestational age; RCT: randomized clinical trial; NM: not mentioned; EG1: exercise group 1; EG2: exercise group 2.

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Table 2: Characteristics of interventions and their results

Intervention							Outcome	
Studies	**EG**	**CG**	**Intensity**	**Weekly frequency**	**Segment time**	**Applicator**	**Outcome Measures**	**Comparison**
Vignochi *et al.* 2012[29]	Passive flexion and extension movements + gentle joint compression at the end of each movement	*NM*	10 rep. Per joint (wrist, elbow, shoulder, ankle, knee, and hip) +/- 15 minutes	5x	Up to 2000g GC: 25.87 days EG: 24.73 days	Physiotherapist	BAP DPD Calcium PTH	**E>C** **E<C** **E=C** **E=C**
Aly *et al.* 2004[30]	Flexion/extension movements associated with gentle compression on joints + full body massage	*NM*	5 rep. Per joint (wrist, elbow, shoulder, ankle, knee, and hip) + 1 minute massage		until reaching 1,800 kg	Not clear	PICP ALP Pyd PITH Calcium	**E>C** **E=C** **E=C** **E>C** **E>C**
Nemet *et al.* 2002[28]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	routine care	5 rep. Per joint (wrist, elbow, shoulder, hip, knee, and ankle	5x	4 weeks	Not clear	BSAP PICP ICTP Weight	**E>C** **E=C** **E<C** **E>C**
Shaw *et al.* 2018[21]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	Just with usual care	5 rep. per joint (wrist, elbow, shoulder, hip, knee, and ankle) 10 to 15 min		Up to 40 weeks (post-menstrual)	Physiotherapist	US ALP Calcium Weight Length Head Circumference	**E=C** **E=C** **E=C** **E=C** **E=C** **E=C**
Erdem *et al.* 2014[12]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	Just with usual care	5 to 8 rep. per joint (wrist, elbow, shoulder, hip, knee, and ankle)	5x	4 weeks	Not clear	US IGF-1 Weight	**E>C** **E>C** **E>C**
Chen *et al.* 2010[22]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	Just with usual care	10 min (wrist, elbow, shoulder, ankle, knee, and hip)	5x	4 weeks	Nurse	US: Without 2 Without 4 Without 6 Without 8 ALP PICP Weight	**E=C** **E=C** **E>C** **E>C** **E=C** **E=C** **E=C**
Tosun *et al.* 2011[23]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	Just with usual care	5 to 8 rep. per joint (wrist, elbow, shoulder, hip, knee, and ankle)	5x	4 weeks	Not clear	US Weight Length Head circumference	**E>C** **E=C** **E=C** **E=C**
Litmanovitz *et al.* 2016[18]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	Just with usual care	5 rep. Per joint (wrist, elbow, shoulder, hip, knee, and ankle) 10 min/day	5x (EG1: 1x/day; EG2: 2x/day)	4 weeks	Nurse and Mothers	US: without 2 without 4 Weight Length Head Circumference	**E1>E2>C E1>C** **E=C** **E=C** **E=C**

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Haley *et al.* 2012[24]	Tactile stimulation/ kinesthetic according to protocol Infant Massage USA	in DD, No stimulation or movement kinesthetic 20 min	20 min/day	6x	15 days	licensed massage therapist	**US** **Pyd** **Dpd** **U- mind oc**	**E>C** **E=C** **E=C** **E>C**
Efe *et al.* 2020[25]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	Clinic Standard Routine	5 to 8 rep. per joint (wrist, elbow, shoulder, hip, knee, and ankle) 7-10 min	*1x day	30 days	Not clear	US Cortisol Weight Length Head Circumference	**E>C** **E=C** **E=C** **E=C** **E=C**
Moyer-Mileur *et al.* 2000[19]	Flexion/extension with passive resistance at the extremities (based on the MOYER-MILEUR protocol)	Tactile Stimulation (no admin activities)	5 to 8 rep. per joint (wrist, elbow, shoulder, hip, knee, and ankle) 5-10 min		until reaching 2,000 kg EG: 26.8 days GC: 23.8 days	Occupational Therapist	DXA Pyd PICP Weight Length	**E>C** **E=C** **E>C** **E>C** **E=C**
Vignochi *et al.* 2008[26]	Flexion/extension with passive resistance at the extremities (based on the Moyer-Mileur protocol)	routine care	10 rep. Per joint (wrist, elbow, shoulder, hip, knee, and ankle) 15 min	5x	until hospital discharge EG: 24.7 days GC: 25.5 days	physiotherapist	DXA BSAP Pyd Calcium Weight Length Head Circumference	**E>C** **E>C** **E<C** **E=C** **E>C** **E=C** **E=C**
González-Agüero *et al.* 2012[27]	Exercises (5 min warm-up, 10-15 exercises, 5 min relaxation)	*NM*	25 min/day	2x	21 weeks	Not clear	total CMO lumbar CMO CMO left hip	**E>C** **E>C** **E>C**
Reza *et al.* 2013[17]	Exercises with weightlifting + Implementation of 200 mg of Ca Ca implementation only exercise Only	*NM*	45 min/day	3x	4 months	Physical educator	**DMO**	**(Ca + Exerc.) > (Exerc.) > (Ca)**
Matute-Llorente et al. 2016[20]	vibrating platform (f: 25 to 30 Hz)	vibrating platform (f: 25 to 30 Hz)	10 repetitions (30-60 seconds)	3x	20 weeks	Not clear	**CMO** **DMO**	**SD < T** **SD < T**

NM: not mentioned; BMC: bone mineral content; BMD: bone mineral density; DD: supine position; US: ultrasound; Ca:

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Figure 2: Measurement of bone formation by the tibial sound velocity (US)

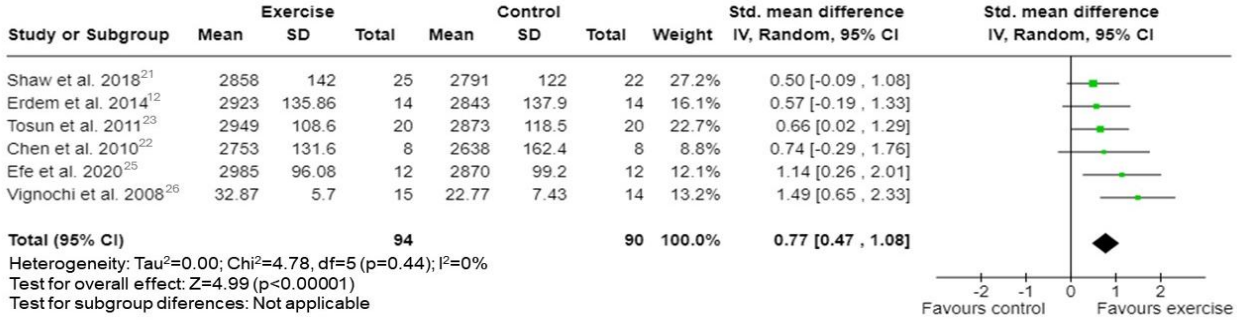

Figure 3: Measurements of bone formation given by biochemical markers of formation

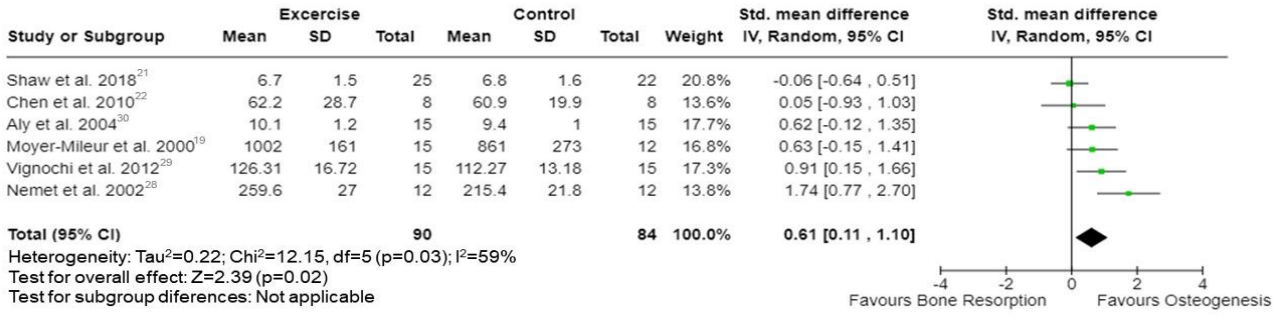

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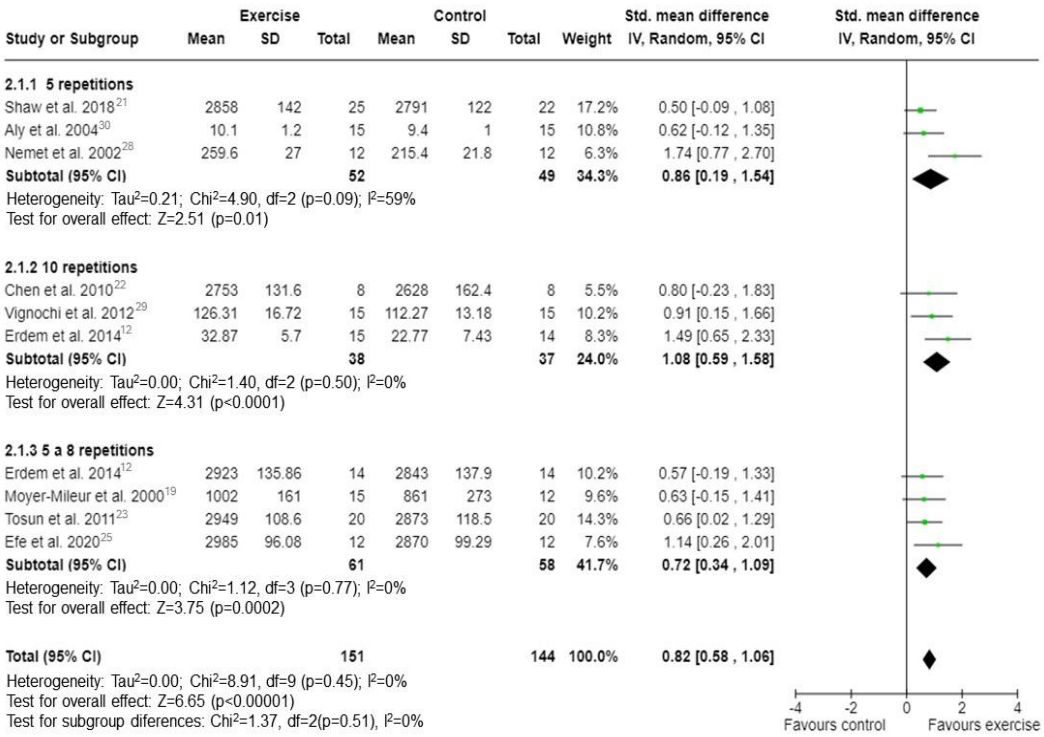
Figure 4: Comparison between the intensities of the Moyer-Mileur et al.



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