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2019

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### Recommended Citation

Constantino, Christopher; Krzak, Joseph; Fial, Alissa; Kruger, Karen M.; Rammer, Jacob; Radmanovic, Katarina; Smith, Peter A.; and Harris, Gerald F., "Effect of Bisphosphonates on Function and Mobility Among Children with Osteogenesis Imperfecta: A Systematic Review" (2019). *Library Faculty Research and Publications*. 109.

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# Effect of Bisphosphonates on Function and Mobility Among Children With Osteogenesis Imperfecta: A Systematic Review

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## ABSTRACT

Osteogenesis imperfecta (OI) is a rare genetic connective tissue disorder that results in bone fragility and deformity. Management is multidisciplinary. Although pharmacologic intervention with bisphosphonates (BP) is a standard of care for individuals with severe OI, no consensus or reviews were found that focus on the effects of bisphosphonates on function and mobility. PubMed, CINAHL, Cochrane Library, Web of Science, and PEDro databases were searched for eligible articles for this review. Methodological quality was assessed using the Cochrane Collaboration's tool for risk of bias. Twenty-six studies (801 children) were reviewed and five showed a low risk of bias. Included studies showed significant variability among clinical protocols for administering BP. Randomized controlled trials did not demonstrate a significant improvement in function and mobility with oral BP administration, whereas nonrandomized open-label uncontrolled studies demonstrated that oral and intravenous BP administration objectively improved function and mobility. The most common outcome measure used by the studies included in this review was the Bleck score. Effect sizes ( $d = 0.28$  to  $4.5$ ) varied among studies. This systematic review also summarized the apparent confounding variables affecting results of previous studies and provided suggestions to improve the quality of future studies. © 2019 The Authors. *JBMR Plus* is published by Wiley Periodicals, Inc. on behalf of the American Society for Bone and Mineral Research.

**KEY WORDS:** OSTEOGENESIS IMPERFECTA; PAMIDRONATE; ALENDRONATE; ZOLEDRONIC ACID; OLPADRONATE; BLECK; PEDI

## Introduction

Osteogenesis imperfecta (OI) is a rare, clinically heterogeneous genetic connective tissue disorder marked by low bone mass and increased bone fragility, resulting in increased susceptibility to fractures, deformities, and substantial growth abnormalities.<sup>(1)</sup> It has a reported incidence of 1 per 10,000 to 20,000 births.<sup>(1–5)</sup> Early genetic studies on OI documented that it is commonly caused by autosomal dominant heterozygous mutations in one of the two genes encoding type I collagen, COL1A1 and COL1A2, and recently, mutations in other genes were documented to be involved in its pathogenesis.<sup>(1–5)</sup> With variable clinical manifestations, OI was initially classified into four types based on severity of signs and symptoms using the Sillence classification system: types I and IV being mild and moderate, type II being lethal, and type III being severe and progressively deforming.<sup>(6,7)</sup> Recent studies have broadened the classification of OI into

up to 19 types based on the genes involved.<sup>(5,8–10)</sup> The classification system by Sillence is still being used in a modified fashion in current studies to stratify subject populations.<sup>(11–14)</sup> As a consequence of the physical impairments brought about by OI, varying degrees of pain,<sup>(11,12)</sup> gait deviations,<sup>(13)</sup> and functional limitations<sup>(11–14)</sup> have also been reported depending on the type and severity of OI. Lower mobility scores,<sup>(11–13)</sup> limited performance of activities of daily living,<sup>(12)</sup> and lower levels of participation in sports, exercise, or physical function<sup>(11–13)</sup> have been reported in individuals with OI. Despite limitations in functional activity, studies show individuals with OI are still able to participate and ambulate in the community but may show difficulty keeping up with typically developing peers.<sup>(12–14)</sup>

Without a genetic cure for OI, management of the disease is aimed at symptom reduction through a multidisciplinary approach consisting of pharmacologic agents, orthopedic interventions, physiotherapy, and rehabilitation.<sup>(15,16)</sup> Among

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Received in original form June 11, 2019; revised form June 19, 2019; accepted June 25, 2019. Accepted manuscript online July 11, 2019.

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JBMR<sup>®</sup> Plus (WOA), Vol. 3, No. 10, October 2019, e10216.

DOI: 10.1002/jbm4.10216

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pharmacologic interventions, bisphosphonates (BP) have been considered standard of care for children with severe OI.<sup>(17–20)</sup> BP can be administered orally or intravenously with varied efficacy, and there are two types, both acting on osteoclasts (cells that break down bone tissue) by disrupting their formation (nitrogenous type BP) or initiating their apoptosis (non-nitrogenous type BP).<sup>(19,21)</sup>

Although BP therapy is widely used to treat OI, results on improvements to function and mobility outcomes have been variable.<sup>(22–24)</sup> Previously published systematic reviews and meta-analyses on BP focused on their effects on increasing bone mineral density and reducing fracture rate. The reports mention function and mobility outcomes, but these were considered secondary variables of interest.<sup>(16,25–27)</sup> To the best of our knowledge, no consensus or systematic reviews have been published to quantitatively describe how BP therapy affects measures of function and mobility among individuals with OI.<sup>(12–14)</sup> Therefore, the purpose of the current work was to systematically review existing literature and describe the effects of BP therapy on improving measures of function and mobility.

## Materials and Methods

### Inclusion criteria

Included studies were limited to populations involving male and female children who have an established diagnosis of OI in which at least one of the outcomes was the effect of bisphosphonates on function and/or mobility using objective outcome measures. Studies that included quality-of-life (QOL) or well-being as outcomes were included if objective parameters of function and mobility were included in the measuring tools used in those studies. Randomized controlled trials (RCTs), non-randomized open-label uncontrolled studies (NROs), NROs with a historic control group, and retrospective studies were included. Non-randomized open-label uncontrolled studies are defined as studies that are not randomized, all subjects are given treatment (no control or placebo group), and both the researchers and subjects are aware of the treatment administered (no blinding).

### Search strategy

We searched the following electronic databases: PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Professions), Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials), Web of Science, and PEDro (Physiotherapy Evidence Database). The initial search strategy was developed in PubMed, using a combination of Medical Subject Terms (MeSH) and key words. Once the initial search was determined, it was modified to fit the parameters of the other databases.

### Selection of studies and data extraction

The two lead authors (CSC and JJK) screened the articles for eligibility independently. In the event of disagreement, a third reviewer (KMK) was included in the discussion until a consensus was reached. A standardized data extraction form was created during study selection and was used to compile relevant descriptive information and relevant data among the included studies.

### Strategy for data synthesis

The reviewers provided a narrative synthesis of the findings from the included studies, structured around OI population type, route (oral or intravenous), dosage of BP administered, and outcomes used to measure function and mobility. Based on the anticipated heterogeneity of outcomes and data completeness, the reviewers provided a summary of intervention effects for each study (Table 1). Effects of BP on measures of function and mobility were calculated with standardized mean differences on each outcome and effect size when applicable.

### Risk of bias (methodological quality) assessment

The two primary reviewers (CSC and JJK) assessed the methodological quality (risk of bias) of the articles independently using the adapted version of the Cochrane Collaboration's tool. This tool reviews five domains, with 11 items. Each item was scored "1" if the item was present in the article, and "0" if it was not (Table 2). Studies fulfilling six or more items were regarded as having a low risk of bias.<sup>(28,29)</sup> Disagreements were resolved by including three reviewers (KMK, JRR, and KR) in the discussion until a consensus was reached. The strength of interrater agreement was measured using Cohen's K coefficient (95% confidence interval), with K=0.41 to 0.60 indicating moderate agreement, K=0.61 to 0.80 indicating good agreement, and K ≥ 0.81 indicating very good agreement.<sup>(28,29)</sup>

### Analysis of subgroups or subsets

Subgroup analyses were performed based on the route of administration (oral or intravenous) of BP, function and mobility outcome measure used, and population.

## Results

Figure 1 illustrates the article selection process. The search strategy yielded 423 articles. Removing duplicates, the number was reduced to 210, and 173 were excluded based on title and abstract. Full texts of the 37 remaining articles were screened, and one was excluded because some participants were given growth hormone in addition to pamidronate, and the results obtained from these participants were not differentiated from those who received pamidronate only.<sup>(30)</sup> Two more were excluded because the main intervention was not bisphosphonate administration.<sup>(31,32)</sup> Six more were excluded because the outcomes used were not objective.<sup>(33–38)</sup> Two more were excluded because they were found to be abstracts presented in proceedings.<sup>(39,40)</sup> A total of 26 full-text articles (801 male and female children) including four RCTs,<sup>(23,41–43)</sup> 17 NROs,<sup>(44,45,47,48,50–55,57,58,60–64)</sup> three NROs with a historic control group,<sup>(49,56,59)</sup> and two retrospective studies<sup>(46,65)</sup> met the inclusion criteria and were included. Population sizes (*n*) ranged from *n*=4<sup>(65)</sup> to *n*=139.<sup>(42)</sup> Three NROs did not specify sex distribution.<sup>(48,51,63)</sup> OI types recruited by most of the studies were I, III, and IV. Other NROs included participants with types V,<sup>(64)</sup> VI,<sup>(57)</sup> VII,<sup>(65)</sup> and VIII.<sup>(53)</sup> Two NROs did not specify the OI type of their population.<sup>(50,60)</sup> Two studies included participants with unclassified types in addition to types I, III, and IV.<sup>(42,54)</sup> One of the retrospective studies recruited only females.<sup>(65)</sup> Bleck score (including its modified forms)<sup>(66,67)</sup> was the most common outcome tool used in 19 (73%) studies, followed by the pediatric disability inventory (PEDI),<sup>(68)</sup> used in six (23%) studies.

**Table 1.** Summary of Study Characteristics and Intervention Outcomes of Included Articles

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Kok 2007 <sup>(41)</sup>	RCT	n = 34 treatment (n = 16) (10 ± 3.1 years old), placebo (n = 18) (11 ± 3.9 years old), 16/18, I (n = 13), III (n = 9), IV (n = 12)	Oral olpadronate, 10 mg/m <sup>2</sup> /d for 2 years	500 mg/m <sup>2</sup> /d calcium, 400 IU/d cholecalciferol	Health-utility index- mark III (HUI), Harter self- perception profile for children (SPCC)	Ambulation (HUI) and athletic performance domain (SPCC): no significant difference from placebo or compared with baseline after 2 years of treatment SPCC was used for participants >6 years old
Sackers 2004 <sup>(23)</sup>	RCT	n = 34 treatment (n = 16) (10 ± 3.1 years old), placebo (n = 18) (11 ± 3.9 years old), 16/18, I (n = 13), III (n = 9), IV (n = 12)	Oral olpadronate, 10 mg/m <sup>2</sup> /d for 2 years	500 mg/m <sup>2</sup> /d calcium, 400 IU/d cholecalciferol	Modified Bleck score Pediatric disability inventory (PEDI)	Modified Bleck score and mobility (PEDI): no significant difference from placebo or compared with baseline after 2 years of treatment
Ward 2011 <sup>(42)</sup>	RCT	n = 139 treatment (n = 109) (11 ± 3.6 years old), placebo (n = 30) (11 ± 4.0 years old), 78/31, I (n = 32), III (n = 39), IV (n = 54) unknown (n = 14)	Oral alendronate, 5 mg/d for patients <40 kg, 10 mg/d for patients ≥40 kg for 2 years	Supplemental Ca and vitamin D were added in quantities to meet the dietary reference intake if the dietary intake was inadequate	PEDI	Of the baseline number of participants, data from only 94 from the treatment group and 28 from the placebo group were obtained due to dropout. Mobility (PEDI): no significant difference from placebo
Seikaly 2005 <sup>(43)</sup>	RCT	n = 20 3–15 years old, 11/9, I (n = 2), III (n = 8), IV (n = 10)	Oral alendronate pulverized into 5 mg (for patients <30 kg) and 10 mg capsules administered with at least 8 ounces of water, 30 minutes before food intake while maintaining an upright position for at least 30 minutes after intake	1000–1300 mg/d calcium, 800– 1200 mg/d phosphorus, and 400 IU vitamin D	PEDI	Patients were treated for 12 months with alendronate then crossed over to placebo and vice-versa. 17 of 20 finished the study. No significant difference in mobility scores between alendronate and placebo (3.00 ± 1.84 versus 2.21 ± 1.00, p = 0.980)
Adiyaman 2004 <sup>(44)</sup>	NRO	n = 8 3.62–13.8 years old, 3/5, III (n = 5), IV (n = 3)	I.v. disodium pamidronate 0.5 mg/kg/d diluted in 150–250 ml saline, over 2 hours for 3 consecutive days spread over a year for a total of 4 cycles	600–800 mg Ca/d through diet and supplements, 4000 IU vitamin D/d	Bleck score	All subjects had a baseline Bleck score of 0. After 1 year of treatment, 5 subjects had a score of 4, 2 had a score of 3, and 1 had a score of 1.

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Falk 2003 <sup>(45)</sup>	NRO	n = 6 1.8–14.7 years old, 3/3, I (n = 1), III (n = 2), IV (n = 3)	i.v. pamidronate 1 mg/kg/d dissolved in 5% dextrose, 25% normal saline to achieve <0.12 mg/mL, over 3 hours for 3 consecutive days every 3.8 months for 2 years. During day 1 of the 1st cycle only, dose was 0.5 mg/kg/d.	Calcium carbonate supplements when calcium intake was insufficient or ionized calcium level below normal	PEDI Serial occupational therapy (OT) evaluations	PEDI scores were inconclusive. Two of the oldest patients (14 and 7 years old) progressed from being wheelchair-dependent to completely ambulatory on OT evaluation.
Alharbi 2008 <sup>(47)</sup>	NRO	n = 27 2.3–12.3 years old, 14/13, I (n = 8), III (n = 9), IV (n = 8), V (n = 2)	i.v. pamidronate disodium diluted in isotonic saline over 3 hours for 3 consecutive days for 2–6 years. Patients 2–4 years old received 0.75 mg/kg/d every 3 months; >4 years old received 1 mg/kg/d every 4 months.	Calcium 1 g/m <sup>2</sup> /d and 1200 IU/d of vitamin D	Bleck score	The overall mobility score improved from 1.8 ± 1.7 to 2.9 ± 1.5 (p = 0.01). A significant 1-point improvement occurred within the first 2 years.
Astrom 2002 <sup>(48)</sup>	NRO	n = 28 0.6–18 years old, sex distribution not stated, I (n = 6), III (n = 10), IV (n = 12)	i.v. disodium pamidronate 10–40 mg/m <sup>2</sup> over 5–8 hour monthly infusions for 2–9 years. For the 1st 3 months, 10 mg/m <sup>2</sup> was given, then 20 mg/m <sup>2</sup> for the next 3 months, and 30 mg/m <sup>2</sup> . Dose was increased to 40 mg/m <sup>2</sup> for 5 children who experienced bone pain. Infusions were preceded with hydration with buffered glucose 25 mg/mL (total dose 500 mL/m <sup>2</sup> for 2–4 hours).	18 subjects were given 1,25-dihydroxycholecalciferol.	Wilson scale Bleck score	Ambulation improved in 21 subjects from a mean score of 8 to 6 on the Wilson scale. Further improvement was noted on 3 on their latest follow-up but the mean Wilson scale score was still 6. 13 of 22 who could not ambulate achieved walking with mean improvement in Wilson scale scores by 2. 15 improved in Bleck scores from 0 to 2 within 2 years and at the latest follow-up. There was no change in the Bleck score of the other 13 subjects. None deteriorated.

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Astrom 2007 <sup>(49)</sup>	NRO with a historic control group	n = 11 treatment (n = 11) (0.5 ± 3.3 years old, historic controls (n = 11) (0.7 ± 0.44 years old), 10/12, I (n = 5), III (n = 9), IV (n = 8)	I.v. disodium pamidronate 10–30 mg/m <sup>2</sup> monthly infusions for 3–6 years For the 1st 3 months, 10 mg/m <sup>2</sup> was given, then 20 mg/m <sup>2</sup> for the next 3 months, and 30 mg/m <sup>2</sup> . Dose was increased to 40 mg/m <sup>2</sup> for 6 children who experienced bone pain. Infusions were preceded with hydration with buffered glucose 25 mg/mL (total dose 500 ml/m <sup>2</sup> for 2–4 hours)	None mentioned	Wilson scale Bleck score	Both outcomes were not applicable at baseline for 9 subjects because they were under 6 months of age. After 1 year of treatment, mean score on the Wilson scale was 6 and mean Bleck score was 1. After 2 years, mean score on the Wilson scale was 4 and mean Bleck score was 2. On the latest follow-up, mean score on the Wilson scale was 3, and mean Bleck score was 3. Scores on latest follow-up were not shown for the control group. It was mentioned that 6 subjects from the control groups lost their previous mobility abilities.
Atta 2014 <sup>(50)</sup>	NRO	n = 72 1–13 years old 40/32, type of OI not specified	I.v. disodium pamidronate diluted in isotonic saline 1 mg/kg/d for 3 consecutive days every 3 months for 2 years	None mentioned	Bleck score	Score improved from 0.94 ± 1.30 to 2.5 ± 1.02 (p < 0.001). Score was 0 in 43 patients at baseline compared with 4 (5.5%) patients at study completion.
Bajpai 2007 <sup>(51)</sup>	NRO	n = 20 4.5 ± 4.2 years old sex distribution not stated, III (n = 13), IV (n = 7)	I.v. pamidronate diluted in isotonic saline 1 mg/kg/d over 3 hours for 3 consecutive days every 4 months for 2–3.8 years until the age of 7.4 ± 4.1 years. During day 1 of the 1st cycle only, dose was 0.5 mg/kg/d.	Oral calcium carbonate 50 mg/kg/d	Bleck score	11 of 20 had ages where scores were applicable at baseline, and 17 had scores applicable at the end. Significantly greater proportion (88.2%) of children had a functional score of 2 or more (able to walk) at last follow-up compared with those at initiation of treatment (45.4%).

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Cho 2005 <sup>(52)</sup>	NRO	n = 16 6.3–15 years old 9/7, I (n = 7), III (n = 2), IV (n = 7)	Oral alendronate 10 mg/d for patients >35 kg, 10 mg every other day for patients weighing 20–35 kg, 10 mg every 3 days for those <20 kg, given at least 1 hour before breakfast, given for 2.1–5.1 years.	Enough dietary calcium and vitamin D were advised but not provided to participants.	Scale devised by the researchers	7 patients had surgical or implant-related problems that may have affected their ambulatory/mobility status. Of the remaining 9, 5 were had improvements on latest follow-up. Among 4 without improvement, 1 with grade 5 started medication 2 years before skeletal maturity, another had leg length discrepancy of 6 cm, 2 were either grade 1 or 2 at the start of medication use.
Garganta 2018 <sup>(53)</sup>	NRO	n = 22 2–21 years old 14/8, I (n = 8), III (n = 7), IV (n = 6), VIII (n = 1)	Pamidronate (n = 16) or zoledronic acid (n = 6) as per the chronic regimen of the patients. I.v. pamidronate diluted 1.1 mg/kg/d every 3 months for patients 2–3 years old, 1.5 mg/kg/d every 4 months for patients aged >3. I.v. zoledronic acid 0.05 mg/kg/d every 6 months for all ages. Mean length of time between the 1st and 2nd infusions was 6.9 months.	None mentioned	Pediatric Quality of Life Inventory 4.0 Generic Core Scales for Physical Functioning (PedsQL)	Results are described in the Discussion section.
Glorieux 1998 <sup>(54)</sup>	NRO	n = 30 3–16 years old 16/14, III (n = 9), IV (n = 9), unclassified type (n = 12)	I.v. disodium pamidronate diluted in 250–500 mL isotonic saline 1.5–3.0 mg/kg/infusion cycle over 4 hours for 3 consecutive days every 6 months initially, then every 4 months for 1.3 to 5 years. 1 had a dose of 3.75 mg/kg/infusion cycle due to a slow response.	800–1000 mg calcium per day through diet and supplementation and 400 IU vitamin D per day	Bleck score	At baseline, 16 were confined to a bed or a wheelchair (score of 0 or 1). Six gained one grade, 5 gained two, and 1 gained three. Four children progressed from being wheelchair-bound (grade 0 or 1) to walking independently (score of 4). In the other 14 children, no change in grade was noticed. Four of those 14 children had a baseline score of 4.

(Continues)



**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Goksen 2006 <sup>(55)</sup>	NRO	n = 16 1.2–1.9 years old 4/12, I (n = 2), III and IV (n = 14)	i.v. disodium pamidronate diluted in 150 mL isotonic saline 7–10 mg/kg/yr monthly at the start, and then was changed to 3–4 mg/kg/yr once a day with 4 cycles/yr because surgeons noticed characteristics of osteoporosis on the femur of 2 patients. Infusion was done over 3 hours and patients were rehydrated with 150 mL isotonic saline before and after therapy. Duration was 0.6–4.7 years (mean 2.50 ± 1.09 years).	800 mg/d calcium and 1000 IU/d vitamin D at the beginning and tapered later according to laboratory changes	Bleck score	14 of 16 completed 1 year of treatment. One patient was not included in the evaluation for mobility because she was under 2 years of age. Ambulation scores increased in 10 children: 4 gained four grades, 6 gained one. In 3 children, no change was noticed. Before therapy, 2 children were fully functional.
Land 2006 <sup>(56)</sup>	NRO with a historic control group	n = 59 0.5–15.7 years old, 29/30, I (n = 18), III (n = 12), IV (n = 29) 48 controls (matched for age and OI type who did not receive pamidronate) were included. No age-matched controls were found for the other 11 subjects who received pamidronate	i.v. pamidronate 0.25 mg/kg on the 1st day, then 0.5 mg/kg on days 2 and 3, then 0.5 mg/kg on all 3 days of subsequent cycles for patients <2 years old. 0.38 mg/kg on the 1st day, then 0.75 mg/kg on days 2 and 3 of the 1st cycle and 0.75 mg/kg on all 3 days of subsequent cycles for those aged 2–3 years. Cycles were repeated every 3 months for patients ≤3 years old. 0.5 mg/kg on the 1st day, then 1 mg/kg on days 2 and 3 of the 1st cycle and 1 mg/kg on all 3 days of subsequent cycles for those >3 years old, with cycles every 4 months. Each dose was diluted in 0.9% saline and administered for 4 hours. Treatment time was 3 years	None mentioned	Modified Bleck score (4-point scale) PEDI	Assessment of functional skills were not performed in children who were younger than 0.6 years (n = 20). Results are described in the Discussion section.

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Land 2007 <sup>(57)</sup>	NRO	n = 10 0.8–14.5 years old, 4/6, VI (n = 10) Other OI types matched for age and criteria reflecting disease severity for comparison type I (n = 3), III (n = 1), IV (n = 6), 0.5–13.9 years old, sex distribution of the comparison group not specified	i.v. pamidronate 0.25 mg/kg on the 1st day, then 0.5 mg/kg on days 2 and 3, then 0.5 mg/kg on all 3 days of subsequent cycles for patients <2 years old. 0.38 mg/kg on the 1st day, then 0.75 mg/kg on days 2 and 3 of the 1st cycle and 0.75 mg/kg on all 3 days of subsequent cycles for those aged 2–3 years. Cycles were repeated every 3 months for patients ≤3 years old. 0.5 mg/kg on the 1st day, then 1 mg/kg on days 2 and 3 of the 1st cycle and 1 mg/kg on all 3 days of subsequent cycles for those >3 years old, with cycles every 4 months. Each dose was diluted in 0.9% saline and administered for 4 hours. Treatment time was 3 years.	Calcium and vitamin D intake were maintained adequate according to the recommended daily allowance.	Modified Bleck score (4-point scale) PEDI	The average level of ambulation improved in OI type VI subjects (baseline: 2.2 ± 1.2, after treatment 2.9 ± 1.2) but was lower than in the comparison group (baseline: 3.3 ± 0.5, after treatment: 3.8 ± 0.4) both before and after treatment. Gross motor function of the subjects with OI type VI assessed by the PEDI score improved during pamidronate treatment but was inferior compared with the comparison group.
Lowling 2007 <sup>(58)</sup>	NRO	n = 43 0.3–16 years old 21/22, I (n = 15), III (n = 13), IV (n = 15)	After i.v. hydration with buffered glucose 25 mg/mL (500 mL/m <sup>2</sup> for 2–4 hours), i.v. disodium pamidronate was given once a month with an increasing dose from 10 to 30 mg/m <sup>2</sup> over 4–8 hours for 1 year.	None mentioned	Functional and caregiver assistance scales of the PEDI	Improvement was found after 1 year of treatment (p < 0.001). Mobility improved in 40 of 43 children. 2 of the 3 who did not improve had recurrent fractures and intramedullary rodding surgery. The third child had maximum scores pretreatment.

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Munns 2005 <sup>(59)</sup>	NRO with a historic control group	n = 58 treatment (n = 29) (2 weeks to 23 months old), 15/14, I (n = 13), III (n = 9), IV (n = 12) Historical untreated control group matched for age and OI type (n = 29)	i.v. pamidronate, 3 consecutive days/3 years. Patients received 0.25 mg/kg on the 1st day of the first cycle, 0.5 mg/kg on days 2 and 3 of the 1st cycle, and 0.5 mg/kg daily on all 3 days in subsequent cycles. Cycles were repeated every 2 months. After the 2nd birthday, treatment was continued with cycles of 0.75 mg/kg pamidronate daily on 3 successive days that were repeated every 3 months. >3.0 years of age, pamidronate dose was 1 mg/kg daily for 3 days, and cycles were repeated every 4 months. Each dose was diluted in 0.9% saline solution and administered slowly over 4 hours.	Calcium intake was maintained adequate according to the recommended daily allowance.	Modified Bleck score (4-point scale) PEDI	Both Bleck (2.3 ± 1.0 versus 0.8 ± 1.0 for controls) and PEDI gross motor scores (36 ± 13 versus 24 ± 12 for controls) were significantly greater in the pamidronate group (p < 0.001).
Salehpour 2010 <sup>(60)</sup>	NRO	n = 64 21 months to 10 years old, 35/29 n = 53 had severe OI (specific OI type not specified)	i.v. pamidronate bisodium 1 mg/kg/d diluted in 250–500 mL normal saline over 4 hours/3 consecutive days every 4 months for 1 to 2 years. If response was slow, dose was increased to 2 mg/kg/d.	Ca through diet with administration of 250–500 mg calcium and 200 IU vitamin D as daily oral supplements	Bleck score	Scores improved (p < 0.05) in all but 3 children. These 3 had an increase of 0 but did not have a decrease of scores.
Sanchez-Sanchez 2015 <sup>(61)</sup>	NRO	n = 14 6 months to 14 years old, 8/6, I (n = 6), III (n = 6), IV (n = 2)	i.v. zoledronic acid 0.05 mg/kg over 1–2 hours every 6 months. Treatment doses received by patients varied.	4 received Ca, 4 received calcitriol, and 4 received both	Modified Bleck score (9-point scale)	Mean Bleck score before treatment was 4 (range 1–9) and was 6 (range 2–9) after treatment (p = 0.001).

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Vyskocil 2005 <sup>(62)</sup>	NRO	n = 30 4–16 years old 16/14, I (n = 22), III (n = 2), IV (n = 6)	Oral alendronate 5 mg/d (patients aged 4–10 years) and 10 mg/d (>10 years of age) for 3 years.	Ca, Mg, vit D, antacids, tetracyclines, or sucralfate 2 hr after BP intake	Bleck score	Bleck scores were $2.57 \pm 1.15$ pretreatment, $3.68 \pm 0.95$ after 3 years, $p = 0.00001$ .
Zacharin 2002 <sup>(63)</sup>	NRO	n = 18 1.4–14.5 years old, sex and type (III and IV) distribution not specified	I.v. disodium pamidronate diluted in 200–500 mL normal saline 1 mg/kg/d over 2–3 hours for 3 days every 4 months for 2 years	None mentioned	Bleck score	11 of 18 children completed treatment. Mobility increased in all patients.
Zeitlin 2006 <sup>(64)</sup>	NRO	n = 11 1.8–15 years old 5/6, V (n = 11) Other OI types matched for age and criteria reflecting disease severity for comparison type I (n = 1), III (n = 1), IV (n = 9) 2.2–15.9 years old Sex distribution of the comparison group not stated	I.v. pamidronate 0.25 mg/kg on the 1st day, then 0.5 mg/kg on days 2 and 3, then 0.5 mg/kg on all 3 days of subsequent cycles for patients <2 years old. 0.38 mg/kg on the 1st day then 0.75 mg/kg on days 2 and 3 of the 1st cycle and 0.75 mg/kg on all 3 days of subsequent cycles for those aged 2–3 years. Cycles were repeated every 12 months for patients $\leq 3$ years old. 0.5 mg/kg on the 1st day, then 1 mg/kg on days 2 and 3 of the 1st cycle and 1 mg/kg on all 3 days of subsequent cycles for those >3 years old, with cycles every 4 months. Each dose was diluted in 0.9% saline administered for 4 hours. Treatment time was 2 years.	Calcium and vitamin D intake were maintained adequate according to the recommended daily allowance.	Bleck score	During the study period, ambulation score improved in 4 patients with OI type V and remained unchanged in 1 patient. One patient was not assessed because of young age. The other 5 patients were independent walkers (grade 4) before pamidronate treatment was started and remained so during the observation interval. In the control group, 4 patients gained 1 to 3 grades, and in 2 patients no progress was noted. The other 5 patients were independent walkers before and after 2 years of treatment.

(Continues)

**Table 1.** (Continued)

Author, year	Study design	n, male/female, OI type	BP type, route, dosage, and duration	Other treatments	Outcome measure/s	Results
Cheung 2009 <sup>(65)</sup>	R	n = 4 Type VII (n = 4) (3.9–12.7 years old), other OI types for comparison (I, III, IV) (n = 8) (0.5 ± 3.3 years old) 3.9–12.7 years old All female	i.v. pamidronate 1 mg/kg/d over 3 hours for 3 consecutive days every 4 months for 2–3.8 years until the age of 7.4 ± 4.1 years. During day 1 of the 1st cycle only, dose was 0.5 mg/kg/d.	Calcium and vitamin D according to the recommended daily allowance	Modified Bleck score (4-point scale) PEDI	Mean Bleck score of the type VII group was 3.25 ± 1.50 and was 3.50 ± 1.00 at the end. Mean Bleck score of the group with other types of OI was 3.50 ± 1.70 and was 3.75 ± 0.71. PEDI scores did not reach statistical significance.
Oztemur 2012 <sup>(46)</sup>	R	n = 7 13–18 years old, 6/1, 1 (n = 7)	i.v. pamidronate disodium 0.75 mg/kg as a single dose over 8 hours every 6 months in saline solution. Number of doses of treatment varied.	800–1200 mg calcium and 400 IU vitamin D	Modified Bleck score	Number of doses of the treatment received by each patient varied.  # of doses Bleck score improvement 1 8 → 9 3 9, no change 5 5 → 9 5 6 → 9 8 8 → 9 10 4 → 6 20 2 → 9

RCT = Randomized controlled trial; NRO = non-randomized open-label uncontrolled study; R = retrospective study; i.v. = intravenous administration.

**Table 2.** Risk of Bias (Methodological Quality) Assessment

Study	A	B	C	D	E	F	G	H	I	J	K	Total
Adiyaman et al. <sup>(44)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Alharbi et al. <sup>(47)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Astrom et al. (2002) <sup>(48)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Astrom et al. (2007) <sup>(49)</sup>	0	0	0	0	0	1	1	0	1	1	1	5
Atta et al. <sup>(50)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Bajpai et al. <sup>(51)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Cheung et al. <sup>(65)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Cho et al. <sup>(52)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Falk et al. <sup>(45)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Garganta et al. <sup>(53)</sup>	0	0	0	0	0	0	0	0	1	1	1	3
Glorieux et al. <sup>(54)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Goksen et al. <sup>(55)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Kok et al. <sup>(41)</sup>	1	1	1	1	0	1	1	0	1	1	1	9
Land et al. (2006) <sup>(58)</sup>	0	0	0	0	0	1	1	0	1	1	1	5
Land et al. (2007) <sup>(57)</sup>	0	0	0	0	0	1	1	0	1	1	0	4
Lowing et al. <sup>(58)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Munns et al. <sup>(59)</sup>	0	0	0	0	0	1	1	1	1	1	1	6
Oztemur et al. <sup>(46)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Sakkers et al. <sup>(23)</sup>	1	1	1	1	1	1	1	1	1	1	1	11
Salehpour et al. <sup>(60)</sup>	0	0	0	0	0	1	0	0	1	1	0	3
Sanchez-Sanchez et al. <sup>(61)</sup>	0	0	0	0	0	1	0	0	0	1	0	2
Seikaly et al. <sup>(43)</sup>	1	1	1	1	1	1	1	0	1	1	1	10
Vyskocil et al. <sup>(62)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Ward et al. <sup>(42)</sup>	1	1	1	1	1	1	1	1	1	1	1	11
Zacharin et al. <sup>(63)</sup>	0	0	0	0	0	1	0	0	1	1	1	4
Zeitlin et al. <sup>(64)</sup>	0	0	0	0	0	1	1	0	1	1	0	4

A = adequate randomization; B = concealed treatment allocation; C = patients blinded; D = care providers blinded; E = outcome assessors blinded; F = drop-out described and acceptable; G = participants analyzed in allocated groups; H = groups similar at baseline; I = cointerventions avoided or similar; J = acceptable compliance in all groups; K = similar timing of outcome assessment in all groups.

Risk of bias (methodological quality) assessment

Summary of scores of the adapted Cochrane Collaboration’s tool is shown in Table 2. Interrater agreement was very good (K = 0.94). Five studies scored ≥6 (low risk of bias).<sup>(23,41–43,59)</sup>

Studies demonstrating a positive effect of bisphosphonates on function and mobility

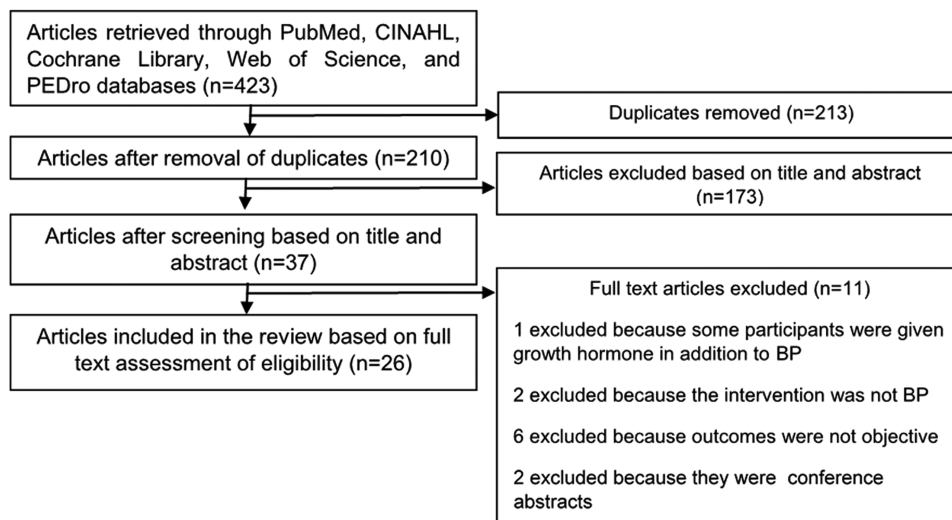
*Oral bisphosphonate administration*

Two NROs administered oral alendronate on patients with OI types I, III, and IV.<sup>(52,62)</sup> Cho and colleagues<sup>(52)</sup> measured function and mobility in 16 patients using a scale the researchers devised themselves. This scale was a 9-point scale, with a highest possible score of 1 (able to sprint and participate in contact sports) and a lowest possible score of 9 (wheelchair- or bedridden; always requiring assistance from others, including self-care activities). Seven of their patients had surgical or implant-related problems that may have affected their ambulatory/mobility status. Of the remaining nine that did not have problems, five had improved scores on latest follow-up. Vyskocil and colleagues<sup>(62)</sup> used Bleck scores of 30 patients and reported significant improvement in mobility ( $2.57 \pm 1.15$  to  $3.68 \pm 0.95$  after 3 years;  $p = 0.00001$ ) with an effect size (Cohen’s D, *d*) of 2.39.

*Intravenous bisphosphonate administration*

Most of the studies (69%) included in this review<sup>(44–51,54–60,63–65)</sup> used intravenous pamidronate, administered at varying doses, with durations ranging from 2 to 8 hours over 1 to 3 consecutive days every 3 to 6 months, administered between 1 and 10 years based on the participants’ needs. Table 1 shows detailed dosages and treatment regimens used by each study.

Bleck score: Adiyaman and colleagues<sup>(44)</sup> found significant increases with a large effect size among their population ( $n = 8$ ), all having Bleck scores of 0 at baseline, increasing to a mean score of  $3.38 \pm 1.06$  after 1 year of treatment ( $d = 4.50$ ). Oztemur and colleagues<sup>(46)</sup> administered treatment at varying doses and all showed varying increases in scores (Table 1). Alharbi and colleagues<sup>(47)</sup> showed improvement in 27



**Fig. 1.** Article selection process.

participants from  $1.8 \pm 1.7$  to  $2.9 \pm 1.5$  ( $p = 0.01$ ,  $d = 0.78$ ). Atta and colleagues<sup>(50)</sup> reported improved scores from  $0.94 \pm 1.30$  to  $2.5 \pm 1.02$  ( $p < 0.001$ ,  $d = 1.03$ ) among 72 patients. Bajpai and colleagues<sup>(51)</sup> noted improvement from  $1.36 \pm 1.12$  to  $2.53 \pm 1.18$  ( $d = 1.23$ ) among 17 participants. Astrom and colleagues<sup>(48)</sup> measured mobility using the Wilson scale (unpublished scale used in Sweden that has a highest score of 1 and lowest of 9) and the Bleck score. They reported improvements in both outcome measures (Bleck:  $0.68 \pm 1.22$  to  $1.57 \pm 1.26$ ; Wilson:  $7.04 \pm 2.50$  to  $4.86 \pm 2.65$ ), with effect size smaller on the Bleck scores ( $d = 0.28$ ) compared with the Wilson scale ( $d = 0.91$ ).<sup>(48)</sup> Land and colleagues performed two studies in 2006<sup>(56)</sup> and 2007.<sup>(57)</sup> In their earlier study, they reported changes from baseline Bleck scores among 59 patients who received 3 years of intravenous BP. Their results showed increased scores from baseline ( $0.84 \pm 1.19$  to  $1.90 \pm 1.25$  after 3 years of treatment;  $p < 0.001$ ,  $d = 0.58$ ). In their later study,<sup>(57)</sup> they compared Bleck scores among 10 patients with OI type VI versus age- and disease severity-matched patients with types I, III, and IV. They found increased scores after treatment in both groups but with lower scores among type VI patients compared with those with types I, III, and IV ( $2.9 \pm 1.2$ ;  $p < 0.05$ ,  $d = 1.42$  versus  $3.8 \pm 0.4$ ;  $p < 0.05$ ,  $d = 7.29$ ). Zeitlin and colleagues<sup>(64)</sup> compared scores among 11 patients with OI type V versus age- and disease severity-matched patients with types I, III, and IV, and reported improved scores among type V patients  $2.7 \pm 1.7$  at baseline to  $3.3 \pm 1.3$  after treatment ( $p < 0.05$ ,  $d = 0.83$ ). The scores of these patients were lower than the control group of types I, III, and IV that had baseline and post-treatment means of 3 and 4, respectively. Cheung and colleagues<sup>(65)</sup> retrospectively reviewed 4 patients with OI type VII versus age- and disease severity-matched patients with types I, III, and IV and reported non-significant increases in both groups. Glorieux and colleagues<sup>(54)</sup> noted improvement in 16 of 30 participants. Goksen and colleagues<sup>(55)</sup> noted improvement in 10 of 14 participants. Salehpour and colleagues<sup>(60)</sup> noted improvement in 59 of 64 participants. Among the participants who had no improvement in these three studies, their Bleck scores did not change and none had reported lower Bleck scores after treatment. Zacharin and colleagues<sup>(63)</sup> also noted increased Bleck scores among all their 18 participants. Means and individual scores were not available in four studies.<sup>(54,55,60,63)</sup>

PEDI score: Lowing and colleagues<sup>(58)</sup> reported improvement in the mobility domain of the functional and caregiver assistance scales of PEDI after 1 year of treatment in 40 of 43 of their participants ( $p < 0.001$ ). Two of the three who did not improve had recurrent periods with fractures and intramedullary rodding surgery, whereas the other patient already had maximum scores at baseline. The earlier study of Land and colleagues<sup>(56)</sup> reported a significant increase in PEDI scores after 3 years among the 59 patients with OI types I, III, and IV with similar changes from baseline among the types (type I:  $22.7 \pm 18.7$ , type III:  $24.6 \pm 14.5$ , type IV:  $21.9 \pm 15.8$ ; analysis of variance:  $p = 0.59$ ). In their later study, they reported improvement in PEDI scores among OI type VI patients, with their scores being lower than those with types I, III, and IV.<sup>(57)</sup> Munns and colleagues<sup>(59)</sup> reported better scores among those treated with i.v. BP ( $36 \pm 13$  versus  $24 \pm 12$  for controls,  $p < 0.001$ ,  $d = 0.95$ ). Cheung and colleagues<sup>(65)</sup> noted non-significant increases in both groups.

Comparison with a historic untreated population: In another study by Astrom and colleagues,<sup>(49)</sup> they compared Bleck and Wilson scores of patients who received intravenous pamidronate to scores of a historical untreated group. Better scores were found

among patients who received treatment on both Bleck ( $3.0 \pm 0.77$  versus  $0.36 \pm 0.67$  for controls;  $p < 0.001$ ,  $d = 3.63$ ) and Wilson ( $2.82 \pm 2.09$  versus  $7.45 \pm 1.51$  for controls;  $p < 0.001$ ,  $d = 2.55$ ) scores.<sup>(49)</sup> In their 2006 study, Land and colleagues<sup>(56)</sup> compared historic data from 48 untreated patients and compared their scores to 48 age-matched patients who received treatment for 3 years. Their results showed significantly higher Bleck scores among the treatment group ( $2.1 \pm 1.2$ ) versus untreated ( $1.0 \pm 1.2$ ),  $p = 0.001$ . The mobility domain of PEDI was also significantly higher among the treatment group (76.3) versus untreated (58.3),  $p = 0.002$ . Munns and colleagues<sup>(59)</sup> showed increased Bleck scores among 58 treated patients compared with an age-matched historical untreated control group ( $2.3 \pm 1.0$  versus  $0.8 \pm 1.0$ ;  $p < 0.001$ ,  $d = 0.75$ ).

Intravenous zoledronic acid administration: Garganta and colleagues<sup>(53)</sup> used both pamidronate (1.1 mg/kg/d every 3 months for patients 2 to 3 years old; 1.5 mg/kg/d every 4 months for patients aged >3 years old) and zoledronic acid (0.05 mg/kg/d every 6 months) to treat 22 children with OI types I, III, IV, and VIII and used the Pediatric Quality of Life Inventory 4.0 Generic Core Scales for Physical Functioning (PedsQL)<sup>(69)</sup> to measure physical function. The choice of BP was based on what regimen the patients were already taking at the start of the study. Not all patients in this study were able to complete study visits, and only 5 patients had data on all visits. These patients had significant changes in scores from the first visit to the post-visit with mean PedsQL scores of  $49.48 \pm 25.49$  before infusion and  $57.03 \pm 25.29$  after 4 weeks post-infusion ( $p = 0.007$ ,  $d = 1.24$ ). Physical function improved after the first infusion and diminished to pre-infusion levels during the time of the next infusion. Mean score was  $46.88 \pm 28.13$  by the second infusion ( $p = 0.008$ ,  $d = 0.51$ ). There were no significant differences between patients treated with pamidronate and zoledronic acid with respect to age, sex, or OI type. Sanchez-Sanchez and colleagues<sup>(61)</sup> treated 14 children with OI types I, III, and IV with zoledronic acid 0.05 mg/kg administered over 1 to 2 hours every 6 months with varying treatment durations. The study used the modified Bleck score (9-point scale) and noted improved mean scores of 4 at pretreatment and 6 after treatment ( $p = 0.001$ ).

### Studies demonstrating no effect on function and mobility

All RCTs used oral BP including olpadronate 10 mg/m<sup>2</sup>/d<sup>(23,41)</sup> and alendronate 5 mg/d (patients <40 kg) or 10 mg/d (patients >40 kg).<sup>(42,44)</sup> Kok and colleagues<sup>(41)</sup> used the ambulation domain of the Health-utility index-mark III scale<sup>(70)</sup> and athletic performance domain of the Harter self-perception profile for children<sup>(71)</sup> for participants >6 years old to measure function and mobility. Sackers and colleagues<sup>(22)</sup> used both modified Bleck scores and PEDI. The remaining two RCTs used PEDI.<sup>(42,43)</sup> All RCTs reported no significant difference between treatment and placebo groups. In the 2006 study of Land and colleagues,<sup>(56)</sup> the self-care domain of PEDI (measure of function) was not significant between the two groups. Falk and colleagues<sup>(45)</sup> also noted inconclusive PEDI scores in their study.

## Discussion

The purpose of the current work was to systematically review existing literature describing the effect of BP therapy on measures of function and mobility. The results of this current

review show that children given intravenous BP have increased mobility, as measured by Bleck scores, after treatment. Results also showed that mobility scores were greater in patients with OI type I, III, and IV compared with other types. Moreover, based on the studies by Astrom and colleagues,<sup>(49)</sup> Land and colleagues,<sup>(56)</sup> and Munns and colleagues,<sup>(59)</sup> improvements are expected to be significantly greater than one would expect when compared with a historical untreated population.

All RCTs showed that oral BPs had no significant effect on function and mobility scores between treatment and placebo groups. In contrast, two NROs that used oral alendronate noted improvements in mobility.<sup>(52,62)</sup> Cho and colleagues<sup>(52)</sup> used an unpublished scale that the researchers devised themselves; hence their findings cannot be compared with those from other studies included in this review. Vyskocil and colleagues<sup>(62)</sup> used the Bleck score, which is the scale most of the studies in this review used, and it was also used by one of the RCTs (Sackers and colleagues<sup>(23)</sup>). Comparing these studies, population sizes were close (34 for Sackers and colleagues; 30 for Vyskocil and colleagues), but these studies differed in terms of treatment time (Sackers and colleagues administered for 2 years; Vyskocil and colleagues for 3 years), age group (Sackers and colleagues =  $10 \pm 3.1$  years old; Vyskocil and colleagues = 4 to 16 years old), and drug of choice (Sackers and colleagues used olpadronate; Vyskocil and colleagues used alendronate). Between the two studies, Sackers and colleagues has a lower risk of bias, scoring 11/11 in the Cochrane Collaboration's tool, whereas Vyskocil and colleagues only scored 4/11. All studies that administered BP intravenously were not randomized and uncontrolled, and if control groups were included, they were primarily limited to historical data. The paucity of RCTs in the available literature can be explained by the fact that intravenous BP administration became a standard of care for the management of severe OI before the RCTs were performed; thus, including a placebo or untreated control group in a study of severe OI is problematic. The three studies<sup>(49,56,59)</sup> that collected data from untreated groups obtained the data earlier than the data from the treatment groups, and intravenous BP may have not yet been used during that time. Relatively small sample sizes among the included studies reflect the rarity of OI. An improvement in mobility was consistent among all the NROs that administered intravenous BP and used Bleck scores (including its modified version) to measure mobility.<sup>(44,47-51,54-57,59-61,63,64)</sup> Adiyaman and colleagues<sup>(44)</sup> showed a very large effect size ( $d = 4.5$ ), which can be explained by all his subjects starting with a score of 0 at baseline. In the study by Oztemur and colleagues,<sup>(46)</sup> the varying dosages and the small sample size reduced the power of the findings, but it is still important to note that all patients either improved or retained their baseline mobility scores and none had a decrease after treatment. Alharbi and colleagues<sup>(47)</sup> reported a moderate effect size ( $d = 0.78$ ), which can be explained by a number of poor responders to treatment. The overall effect to mobility, however, was still an increase. The Wilson scale that Astrom and colleagues used in both their studies is unpublished and has not been verified or tested for reliability, but since both studies also used Bleck, findings from both studies also contribute to the overall improved mobility scores found in this review.<sup>(48,49)</sup> Moreover, it is consistent in all studies that treatment with i.v. BP does not decrease function or mobility scores. Another consistent finding in this review is that baseline and post-treatment function and mobility scores are higher among patients with types I, III, and IV compared with other types

(types V,<sup>(64)</sup> VI,<sup>(57)</sup> VII<sup>(65)</sup>) as measured by both Bleck<sup>(55,57,64)</sup> and PEDI<sup>(57,65)</sup> scores. Function and mobility scores measured by PEDI were inconsistent. Falk and colleagues<sup>(45)</sup> noted inconclusive results and Cheung and colleagues<sup>(65)</sup> noted non-significant increases in scores, while four other studies<sup>(56-59)</sup> reported improvement after i.v. BP administration. In the study performed by Garganta and colleagues<sup>(53)</sup> using both i.v. pamidronate and zoledronic acid, increased function was noted with the use of the PedsQL scales, but because this is the only study that used this scale, no comparisons with other studies can be made. The retrospective review by Cheung and colleagues,<sup>(65)</sup> which had a sample size of 4 and only included females, was the only study to show non-significant increases in Bleck scores after i.v. BP administration.

Limitations of this review include a high number of studies (81%) with low methodologic quality. In addition, among the studies that administered BP intravenously, only one study had high methodologic quality.<sup>(59)</sup> This could be explained by the Cochrane collaboration tool, which was used to appraise the included studies regarding methodologic quality. As RCTs were included in this review, an appraisal tool specific to RCTs was employed. Because of this, any study that was not an RCT is discredited in five of the 11 categories in the assessment tool. Additionally, most of the studies included in this review scored low on the appraisal tool for not having comparable groups at baseline. This was not because they had different baseline groups, but because they had no control groups since these were single-group studies that tracked changes over time. These were longitudinal studies that lacked comparison.

Another point, which was expected because of the rarity of OI, has made the administration of BP, sample sizes, and follow-up periods very heterogeneous among the included studies. Also, because of the wide ranges of age groups and differences in demographic profiles and OI types, findings in the studies may not have enough power to draw strong correlations. Lastly, some studies included in this review may have been underpowered for outcome measures related to function and mobility. Most of the included studies were powered based on a primary outcome of bone mineral density. Therefore, we are uncertain if sufficient sample sizes were recruited in all studies to identify an effect of bisphosphonates on the chosen measures of function and mobility.

Hence, it is advised that our results be interpreted with caution because of these limitations. We suggest that future studies be conducted among comparable cohorts at baseline by ensuring participants with similar ages, OI types, and functional status at baseline to reduce confounding variables that may affect the outcome of these studies. Furthermore, these populations should receive consistent treatment regimens and durations of BP administration in order to draw stronger conclusions regarding the effectiveness of BP administration on improving function and mobility. Although intravenous BP is the standard of care and RCTs involving placebo controls are not possible, controlled studies that compare dosage regimens or combinations of BP treatment with other modalities like physical therapy are also suggested. It is suggested that better-powered studies on the effect of BP on function and mobility among children with OI be performed in the future.

This review, however, cannot answer which i.v. BP dosage best improved mobility because of the heterogeneous studies included, and future studies with more consistent dosages and treatment times with bigger and more homogeneous samples that measure mobility using the Bleck score are suggested.



## Disclosures

All authors state that they have no conflicts of interest.

## Acknowledgments

This review was conducted with support from the Department of Health and Human Services (HHS)/National Institute on Disability, Independent living, and Rehabilitation Research (NIDILRR), Advanced Rehabilitation Research Training (ARRT), grant no. 90AR5022-05-00. This work has not been published elsewhere and it has not been simultaneously submitted for publication elsewhere. All tables and figures are the original work of the authors and no permissions were required.

Before the completion of this review, the protocol was registered to PROSPERO (International prospective register of systematic reviews), ID # CRD42019120922, and can be viewed in the following link: [https://www.crd.york.ac.uk/PROSPERO/display\\_record.php?RecordID=120922](https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=120922).

Authors' roles: CSC is the primary author and drafted the manuscript. AVF created and ran the search strategy on all the databases mentioned and wrote the verbiage for it. The full search strategy can be viewed in the following link: [https://www.crd.york.ac.uk/PROSPEROFILES/120922\\_STRATEGY\\_20190102.pdf](https://www.crd.york.ac.uk/PROSPEROFILES/120922_STRATEGY_20190102.pdf). CSC and JJK screened the articles for inclusion and risk of bias. KMK, JRR, and KR helped resolve disagreements between CSC and JJK. PAS, GFH, and all the coauthors had a chance to review and edit this manuscript before submission, and CSC incorporated all the comments and edits of all the authors. CSC accepts responsibility for the manuscript's integrity, including data analysis.

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