



Treatment of Pre-Collapse Stages of Osteonecrosis of the Femoral Head: a Systematic Review of Randomized Control Trials

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Abstract *Background:* Treatment for osteonecrosis of the femoral head (ONFH) remains controversial. Current reviews include low-level evidence studies evaluating the treatment of both pre-collapse and collapse stages of the disease. *Questions/Purposes:* The purpose of the current study is to systematically review the literature evaluating core decompression (CD) with bone marrow mesenchymal cells (BMMCs), CD alone, and bisphosphonate treatment in pre-collapse ONFH by focusing just on randomized clinical trials (RCTs) reporting functional and radiologic outcomes. We aim to determine if the literature provides evidence supporting any single approach. *Methods:* Using PubMed and EMBASE databases, we reviewed the clinical evidence of treatments for pre-collapse ONFH following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Twelve RCTs met the inclusion criteria. *Results:* Results showed that CD with BMMCs has lower risk of femoral head collapse when compared to the CD alone excluding hips lost to follow-up (relative risk (RR) [95% CI]:0.25 [0.11, 0.60]; $p=0.002$) and when assumed that hips lost to follow-up experienced collapse (RR [95% CI]: 0.11 [0.03, 0.47]; $p=0.003$). Neither CD nor bisphosphonate treatments showed lower risk to femoral head collapse when compared to control treatments ($p=0.46$ and 0.31 , respectively) *Conclusion:* Current

literature shows that there is a lower risk of femoral head collapse in patients with ONFH treated with CD combined with BMMCs when compared to CD alone; however, there is no robust evidence to determine the effect on functional outcomes. More RCTs assessing new combination therapies and using standardized outcome measures are required.

Keywords osteonecrosis · femoral head · pre-collapse treatment

Introduction

Osteonecrosis of the femoral head (ONFH) has become an increasingly common disease with an incidence of 20,000–30,000 in the USA [52]. Although both traumatic and atraumatic factors have been identified as risk factors, the etiology of ONFH remains unclear. The most frequent risk factors for ONFH in the USA include alcohol (20–40%), corticosteroid therapy (35–40%), and idiopathic (20–40%) [47]. One of several theories proposes that ONFH is a disease resulting from impaired blood supply to the femoral head, which leads to osteocyte death, defective bone repair, and collapse of the architectural bone structure [10, 37]. Impaired vascular supply can result from external or internal vascular insult caused by direct injury, thrombotic intravascular occlusion, or extravascular compression [19, 21, 35]. There are several mechanisms that can lead to vascular occlusion resulting in ONFH. High-dose steroid administration and alcohol abuse have been found to alter circulating lipids leading to resultant microemboli in the arteries supplying the bone [22]. Disease processes that increase intravascular coagulation and thrombus formation can also lead to vascular damage. Occlusion can result from red blood cell sickling as seen in hemoglobinopathies, accumulations of cerebroside-filled cells within the bone marrow as seen in Gaucher's disease, and nitrogen bubble formation as seen in Caisson disease [20]. Trauma such as fracture or dislocation primarily in the subcapital region of the femoral neck can

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also lead to compromised blood flow to the femoral head [20]. In some cases where no cause can be identified, it is considered of idiopathic origin [5, 35, 50].

ONFH commonly affects patients between 30 and 50 years of age and progresses to complete collapse in 80% of untreated patients [31, 52]. Therefore, early diagnosis is critical to halt or reverse the progression of the disease, ultimately preventing collapse and the need for total hip replacement (THR). Clinically, patients can initially present asymptotically but, as the disease progresses, can develop groin pain radiating to the knee or buttock as well as limited hip range of motion and pain with forced internal rotation [20]. Diagnostic modalities available include radiography, scintigraphy, functional bone evaluation, magnetic resonance imaging (MRI), computer-assisted tomography, and histological studies. Current ONFH diagnosis is dependent upon plain AP and frog-leg lateral radiographs of the hip, followed by MRI. Pre-collapse joint-preserving treatments include nonweight bearing (NWB) therapy, physical therapy, extracorporeal shock wave therapy (ESWT), hyperbaric oxygen (HBO), bisphosphonates, core decompression (CD) with or without concentrated stem cells, bone grafting, and osteotomy procedures [35, 43, 50]. Unfortunately, the optimal treatment for pre-collapse ONFH has not yet been identified [52].

Current reviews in ONFH include studies with level I to level IV evidence evaluating different treatment options for pre-collapse and post-collapse lesions [12, 20, 28, 30, 40, 50]. To our knowledge, there is no systematic review of high-level evidence studies that attempts to quantitatively analyze the outcomes of the different treatments for pre-collapse stage ONFH. The purpose of the current study was to systematically review the literature evaluating the clinical evidence for CD with bone marrow mesenchymal cells (BMMCs), CD alone, and bisphosphonate treatment in pre-collapse ONFH by focusing on randomized clinical trials (RCTs) reporting both radiologic and functional outcomes. Our primary comparative outcomes were rates of femoral head collapse and need for THR. We aimed to determine if there is literature support for a treatment that delays progression to femoral head collapse and THR and improves functional outcomes when compared to other treatment regimens.

Methods

A systematic review of two electronic databases, PubMed and EMBASE, was conducted using the following search terms: “(avn OR avascular necrosis OR osteonecrosis OR osteonecrosis of femoral head OR onfh) AND (femoral head OR hip OR femur) AND (bisphosphonates OR forteo OR pth OR parathyroid hormone OR teriparatide OR coring OR core decompression OR stem cells OR drilling OR free vascularized fibular graft OR bone graft)”. Limits used were English and humans. The search was performed on February 10, 2016.

Inclusion criteria included (1) RCTs on treatments for pre-collapse ONFH, (2) reported functional and radiologic

outcomes, (3) human studies, (4) published in a peer-reviewed journal, (5) comparison groups of ≥ 10 hips, and (6) those written in English. No publication date restrictions were imposed. Exclusion criteria included (1) in vitro studies, (2) post-collapse treatment, (3) studies performed in the pediatric population, (4) studies reporting subchondral insufficiency fracture or transient marrow edema, and (5) studies comparing different surgical techniques or different grafts (vascularized fibular grafts versus nonvascularized fibular grafts).

Two independent reviewers systematically performed the eligibility assessment (***) and (***). Reference lists of selected articles were also reviewed to ensure that no pertinent articles were omitted. Disagreements between reviewers were resolved through consensus, and a third reviewer (***) was consulted if no consensus was reached.

A data extraction sheet was developed and pilot-tested for five randomly selected included studies and refined accordingly. Two reviewers performed data extraction independently in included trials on (1) demographic characteristics of participants, (2) type of intervention, (3) radiologic and functional outcomes, and (4) length of follow-up. Disagreements were resolved by discussion. If agreement was not reached, a third author made the final decision (***). A fourth reviewer with experience in ONFH performed a final check on all data (***) .

To evaluate validity of eligible RCTs, two reviewers (***) and (***) determined adequacy of randomization, concealment of allocation, blinding, and the extent of loss of follow-up according to Cochrane Collaboration’s Risk of Bias Tool for randomized controlled trials [17].

Studies were categorized into the following groups: (1) CD with BMMCs versus CD alone, (2) CD alone versus conservative treatment, (3) bisphosphonates versus control (conservative treatment, placebo, or electroshock wave therapy [ESWT]), or (4) CD with alendronate versus CD alone. Qualitative and quantitative analysis for radiologic and functional outcomes in each group was done if possible. Treatment complications were also reported.

Statistical Analysis

Effect sizes are expressed as risk ratios with 95% confidence intervals for each study. Random-effects method was calculated for each treatment comparison using the Mantel-Haenszel method. Study-level and pooled risk ratios are presented in forest plots. When patients were excluded or lost to follow-up in trials after randomization, the study effect size was calculated without these hips and, as a sensitivity analysis, with these hips by considering them as worst possible outcome (i.e., femoral head collapse or THR). Analyses were performed using Revman V.5.3 (Nordic Cochrane Centre, Copenhagen) [41].

Results

The results of the literature search are presented in a flow chart according to the Preferred Reporting Items for

Systematic Reviews and Meta-Analyses (PRISMA) statement [29, 33]. No additional studies were identified by searching the references. Twelve studies were included in the qualitative synthesis and ten in the quantitative analysis (Fig. 1).

All studies [9, 11, 18, 23, 24, 26, 27, 38, 45, 49, 51, 53] reported the stage of ONFH, 592 hips (76%) were classified as stages I and II (Steinberg [48], ARCO [6], or FICAT [7]), and 186 hips (24%) were classified as stage III according with Steinberg classification. One study used Mitchell [32] classification (Table 1). Alcohol was the most common etiology (Fig. 2). Functional and radiologic outcomes are presented in Table 2.

All studies were assessed for risk of bias in their Methods. One study had low risk of bias for all elements [9]. Eight studies had high risk for blinding of participants and personnel [18, 27, 45, 49, 51], and six studies were judged to be high risk of bias for random sequence generation [11, 18, 24, 26, 38, 49]. The randomization methods were described as adequate in five trials. The specific reviewers' judgments for risk of bias are detailed in Fig. 3.

Synthesis of Results

Core decompression (CD) plus BMBCs versus CD alone was compared. CD with BMBC treatment showed a lower risk of femoral head collapse when excluding hips lost to follow-up (relative risk (RR) [95% CI]:0.25 [0.11, 0.60]; $p=0.002$) and when assuming that hips lost to follow-up experienced collapse (RR [95% CI]: 0.11 [0.03, 0.47]; $p=0.003$) (Fig. 4a, b).

No significant difference was seen in the risk ratio for THR when hips lost to follow-up were excluded (RR [95% CI]:0.43[0.14, 1.33]; $p=0.14$) or when assuming that hips lost to follow-up and excluded from analysis required THR (RR [95% CI]:0.29 [0.08, 1.01]; $p=0.05$) (Fig. 5a, b). No complications were reported in either of the groups.

When core decompression (CD) was compared to conservative treatment, quantitative analysis showed no significant difference in the risk of femoral head collapse for CD versus conservative treatment (RR [95% CI]: 0.79 [0.41, 1.49]; $p=0.46$). No significant difference was seen in the risk of THR for CD versus conservative treatment (RR [95% CI]: 0.92 [0.44, 1.93]; $p=0.82$) (Fig. 6a, b). No hips were lost to follow-up or excluded from analysis [24, 38, 49]. Two cases of infection were reported and were treated with antibiotics (CD group).

Bisphosphonate treatment was also compared with control treatment (conservative treatment, placebo, or ESWT).

Group analysis did not show a difference in the risk of femoral head collapse when excluding hips lost to follow-up or excluded from the analysis (RR [95% CI]:0.59 [0.22, 1.61]; $p=0.31$) or when assuming that all hips lost to follow-up or excluded from analysis progressed to collapse (RR [95% CI]: 0.72 [0.37, 1.42]; $p=0.35$) (Fig. 7a, b). Similar results in risk of THR were seen when excluding hips lost to follow-up (RR [95% CI]: 0.65 [0.30, 1.41]; $p=0.28$) and when assuming that all hips lost to follow-up or excluded from analysis progressed to THR (RR [95% CI]: 0.71 [0.39, 1.30]; $p=0.27$) (Fig. 8a, b).

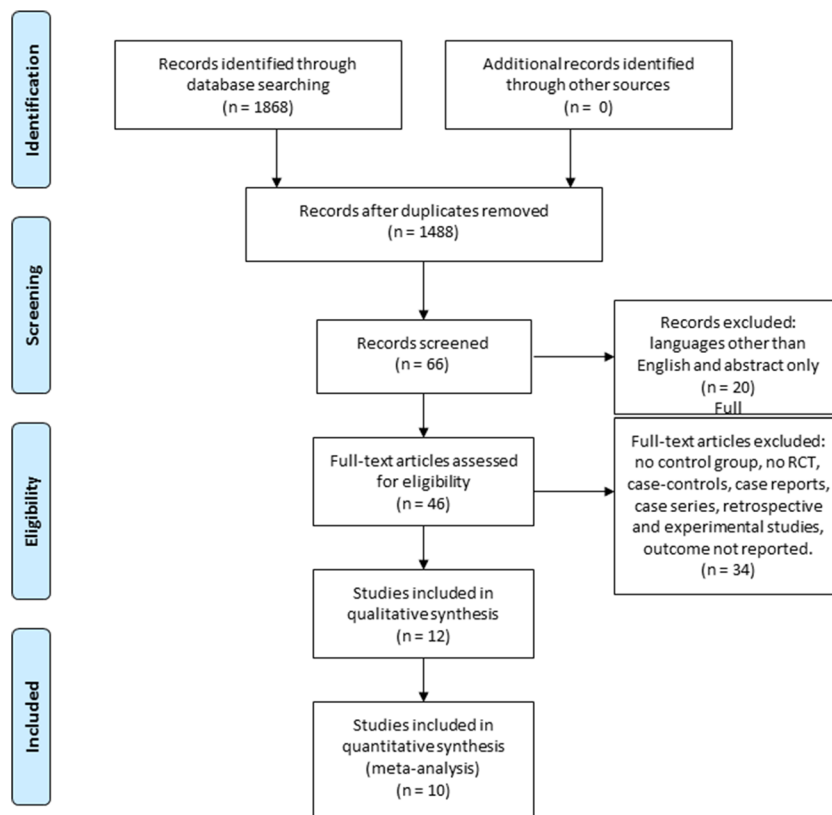


Fig. 1. PRISMA flow diagram.

Table 1 Baseline characteristics of randomized control trials

Study	Study type	Group 1					Group 2				
		Treatment	Patients (hips)	Mean age	Gender (M/F)	Steinberg class (hips)	Treatment	Patients (hips)	Mean age	Gender (M/F)	Steinberg class (hips)
Gangji, 2011 [11]	RCT	CD + BMMCs	13 hips	42.2	^a	I (2), II (11) ^b	CD	11 hips	45.7	^a	I (2), II (9) ^b
Zhao, 2012 [54]	RCT	CD + BMMCs	53 hips	32.7	26:24	I C (3), IIA (15), IIB (23), IIC (10) ^b	CD	51 hips	33.8	27:23	IC (2), IIA (15), IIB (22), IIC (12) ^b
Sen, 2012 [45]	RCT	CD + BMMCs	26 hips	–	19:7	Mitchell–A (7), B (4), C (8), D (1)	CD	25 hips	–	18:7	Mitchell–A (6), B (9), C (11), D (1)
Koo, 1995 [24]	RCT	CD	18 hips	44.83	17:1	I (10), II (7), III (1)	Conservative	19 hips	48.31	17:1	I (12), II (4), III (3)
Neumayr, 2006 [38]	RCT	CD	17 (17)	24.67	8:9	I (2), II (5), III (10)	Conservative	21 (21)	26.41	11:10	I (10), II (11), III (17)
Stulberg, 1991 [49]	RCT	CD	19 (29)	38.6	–	I (10), II (7), III (11) ^c	Conservative	17 (26)	38.6	–	I (5), II (7), III (10) ^c
Chen, 2012 [9]	RCT	Alendronate	26 (32)	48.4	22:4	IIC (20), IIC (12)	Placebo	26 (33)	44.2	19:7	IIC (25), IIC (8)
Lai, 2005 [26]	RCT	Alendronate	20 (29)	42.6	15:5	II (17), III (20)	Placebo	20 (25)	42.4	15:5	II (13), III (20)
Lee, 2015 [27]	RCT	Zoledronate	55 (55)	43.8	39:16	I (29), II (26)	Conservative	55 (55)	45.2	41:14	I (31), II (24)
Hsu, 2010 [18]	RCT	Alendronate + ESWT	28 (50)	39.1	18:10	I (2) II (35) III (13)	EWST	35 (48)	39.6	27:8	I (2) II (27) III (19)
Wang, 2008 [51]	RCT	Alendronate + ESWT	23 (30)	38.6	20:5	I and II (19), III (11) ^b	EWST	25 (30)	35.7	13:10	I and II (25), III (5) ^b
Kang, 2012 [23]	RCT	Alendronate + CD	55 hips	43.8	37:18	IIA (17), IIB (25), III (13) ^c	CD	52 hips	45.3	35:17	IIA (15), IIB (24), III (13) ^c

RCT randomized control trials, CD core decompression, BMMCs bone marrow mesenchymal cells, ESWT electroshock wave therapy

^a Gender is reported for all population: M 9; F 10

^b ARCO classification

^c FICAT classification

The reported etiologies for osteonecrosis of the femoral head

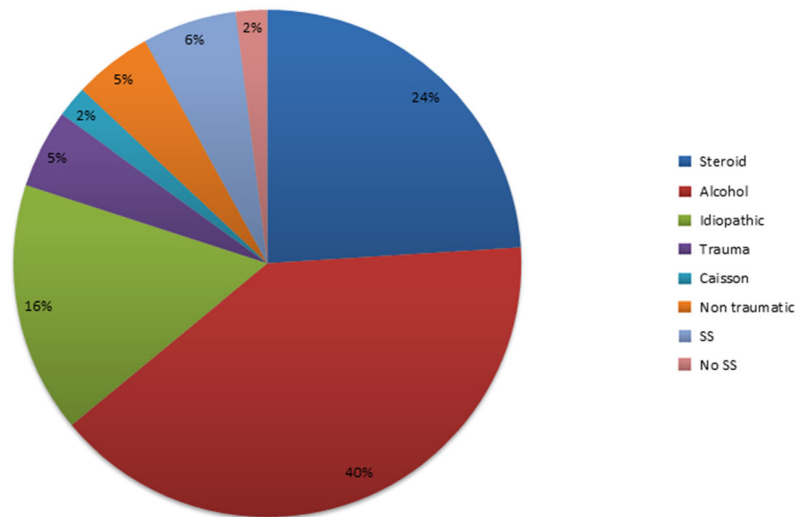


Fig. 2. The reported etiologies for osteonecrosis of the femoral head. SS sickle cell disease.

There was no significant difference in mean HHS at 24-month follow-up (RR [95% CI]: 3.85 [-7.43, 15.13]; $p=0.50$) (Fig. 9). Local complications (swelling and ecchymosis) after ESWT, transient dizziness after HBO, and dyspepsia following alendronate treatment were reported.

Discussion

The goal in treatment of ONFH is to delay progression of the disease and ultimately prevent collapse and THR, especially in the younger population. However, the optimal treatment for pre-collapse ONFH has not yet been identified [52]. This

Table 2 Functional and clinical outcomes

Study	Functional assessment	Outcome	Follow-up time (months)	Radiologic assessment	Outcome	Mean follow-up time (months)
Gangji, 2011 [11]	VAS Lesquene WOMAC	+ + +	24	MRI	Delay to collapse: + Delay to THR: ND	NA
Zhao, 2012 [54]	HHS	+	24	MRI	Delay to collapse: + Delay to THR: ND	NA
Sen, 2012 [45]	HHS	-	24	MRI, X-rays	Delay to THR: -	
Koo, 1995 [24]	MAP	+	13	MRI, X-rays	Delay to collapse: ND Delay to THR: ND	24
Neumayr, 2006 [38]	CHOHES	I	27	MRI, X-rays	Delay to THR: ND	CD group: 37.2 Control group: 36
Stulberg, 1991 [49]	HHS	+	13	MRI, X-rays	Delay to collapse: ND	26.8
Chen, 2012 [9]	HHS SF-36	ND ND	24	MRI, X-rays	Delay to THR: + Delay to collapse: ND Delay to THR: ND	NA
Lai, 2005 [26]	HHS	I	24	MRI, X-rays	Delay to collapse: + Delay to THR: +	8
Lee, 2015 [27]	HHS WOMAC	- -	24 24	MRI, X-rays	Delay to collapse: ND Delay to THR: ND	24
Hsu, 2010 [18]	HHS MAP WOMAC SF-12	- - - -	26	MRI, X-rays	Progression: ND Delay to THR: ND	NA
Wang, 2008 [51]	HHS	-	6.5	MRI, X-rays	Progression: ND	24.87–26.14
Kang, 2012 [23]	HHS	-	15.75	MRI, X-rays	Delay to collapse (+)	62.5

Outcomes: (+) significant improvement, (-) no significant improvement; (ND) no difference, and (I) statistics not reported
 MAP Multidimensional Assessment Pain Scale, WOMAC Western Ontario and McMaster Universities Arthritis, CHOHES Children’s Hospital Oakland Hip Evaluation Scale, HHS Harris Hip Scores, VAS visual analogue score, SF-36 Short-Form 36 Health Survey, SF-12 Short-Form 12 Health Survey

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2012	+	+	+	+	+	+	+
Gangji 2011	-			+		+	+
Hsu 2010	-	-	-	-	+	+	+
Kang 2012	+			+	+	+	+
Koo 1995	-	-	-		-	-	
Lai 2005	-	-	-	+	+	+	+
Lee 2015	+	+	-	+	+	+	+
Neumayr 2006	-	-	-			-	+
Sen 2012	+		-		-	-	+
Stulberg 1991	-	-	-	-	-	+	+
Wang, 2008		-	-	+	+	+	+
Zhao 2012	+	+		+	-	+	+

Fig. 3. Risk of bias summary: review of authors’ judgments about each risk of bias item for each included study. (+): low risk of bias; (-): high risk of bias; (): unknown risk of bias.

systematic review of RCTs quantitatively analyzes radiologic and functional outcomes on CD with BMMCs, CD alone, and bisphosphonate treatment for pre-collapse stage ONFH. We found that CD combined with BMMCs is the only compared treatment that decreased the risk of femoral head collapse in patients with pre-collapse ONFH.

The analysis showed significant difference in the risk for femoral head collapse when comparing CD combined with BMMCs versus CD alone (RR 0.11; $p=0.003$). CD plus BMMC treatment did not reduce the time to THR, even under assumption that all hips lost to follow-up required a THR (RR=0.29; $p=0.05$). It is important to note that for all studies, THR was not the standard treatment for hip collapse, indications for THR were not specified, and one study was excluded from the analysis because failure incidence was not reported [45]. Similar results were reported in previous studies; however, those reviews included level II to level IV evidence studies [28, 35, 40]. It has been reported that the addition of stem cells to CD accelerates fracture healing by differentiating in osteoprogenitor cells required for bone formation [14, 16, 23, 30]. Direct instillation of stem cells through the core tract was the method reported in these studies [11, 53]. Gangji et al. [11] harvested the bone marrow from the iliac crest obtaining a final volume of 49.7 ± 2.3 ml and $1.9 \pm 0.2 \times 10^9$ mononuclear cells, while Zhao et al. [54] harvested the bone marrow cells from the CD tunnels of the subtrochanteric femoral region, cultured for 2 weeks, and injected a total of 2×10^6 BMMCs. Although results proved to be good in both cases, previous studies have shown that a number of mononuclear cells over 5×10^7 are essential in order for this method to be effective [15]. CD plus BMMCs also appears to be a safe procedure that has not carried complications in the RCTs done at the time of this systematic review.

In this study, CD alone showed no significant difference in the risk of collapse or time to THR when compared with conservative treatment at 24-month follow-up. Results are limited by the fact that outcomes were reported as hip survival rate [38, 49] using the end point of no further intervention (THR for patients in the CD group, and CD or THR for patients in the control group). Neither the indication for additional surgery nor the definition of failure was reported. Furthermore, the CD technique was different in each study. Koo et al. [24] used the CD technique as described by Steinberg et al. [48] and filled decompression tunnels with cancellous bone from the trochanteric area. Neumayr et al. [38] used one drill hole directed at the necrotic lesion defined on preoperative MRI, followed by curettage and irrigation. Lastly, Stulberg et al. [49] continuously monitored intra-osseous pressure drilling. However, there is no reported evidence of statistical delay to collapse with any of these techniques when compared with conservative treatment [42, 46]. These negative results using CD alone may be due to destructive resorption without effective consecutive bone formation, as a consequence of decreased proliferation of progenitors [14]. One previously published meta-analysis of 24 studies demonstrated that the best results of CD were in the treatment of early-stage lesions, as 84% of patients with Ficat stage I disease and 65% of patients with stage II disease had successful results; therefore, reported outcomes may be affected by stage of disease [21, 34].

Bisphosphonate treatment inhibits the resorptive activity of mature osteoclasts and reduces the apoptosis in osteoblasts and osteocytes [44]. Since osteoclasts resorb the necrotic bone and weaken the cancellous bone between the viable and the necrotic area [26], bisphosphonates have been

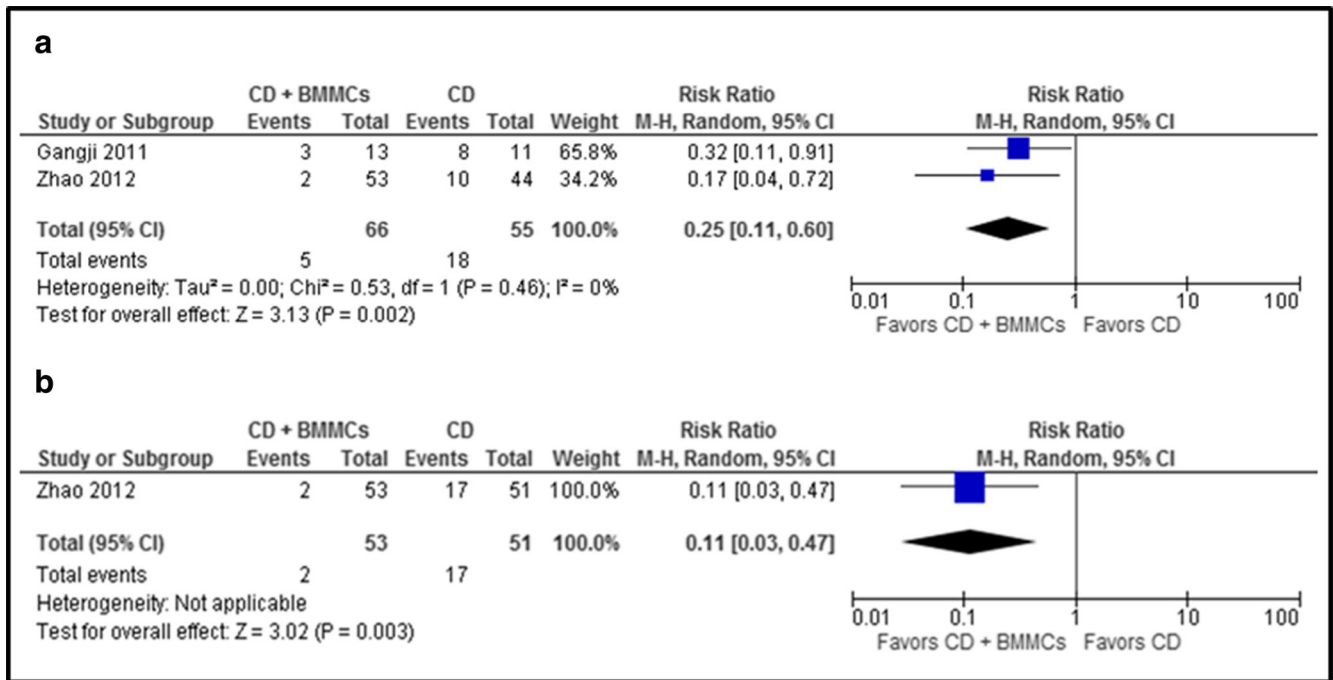


Fig. 4. a, b The graph shows the risk ratio for femoral head collapse for CD plus BMMCs versus CD. **a** Excluding hips lost to follow-up or excluded from analysis. **b** Assuming that all hips lost to follow-up or hips excluded from analysis experienced femoral head collapse (worst-case scenario). Number of events represents the number of hips that progressed to the fractural stage of osteonecrosis (ARCO stage III or more).

used to prevent micro fractures and collapse in cases of ONFH in several studies [1–4]. However, pooled risk ratio of studies comparing bisphosphonates versus control treatments (conservative treatment, placebo, and ESWT) did not show any improvement on radiologic or functional outcomes at 24-month follow-up. Lai et al. [26] reported

positive results after alendronate treatment but included hips that had CD at the beginning or during the study. Contrarily, it was found that neither alendronate [9] nor zoledronate [27] prevents collapse, reduces the incidence of THR, or improves HSS outcome after 2-year follow-up. Alendronate treatment is administered 10 mg per day or 70 mg per week

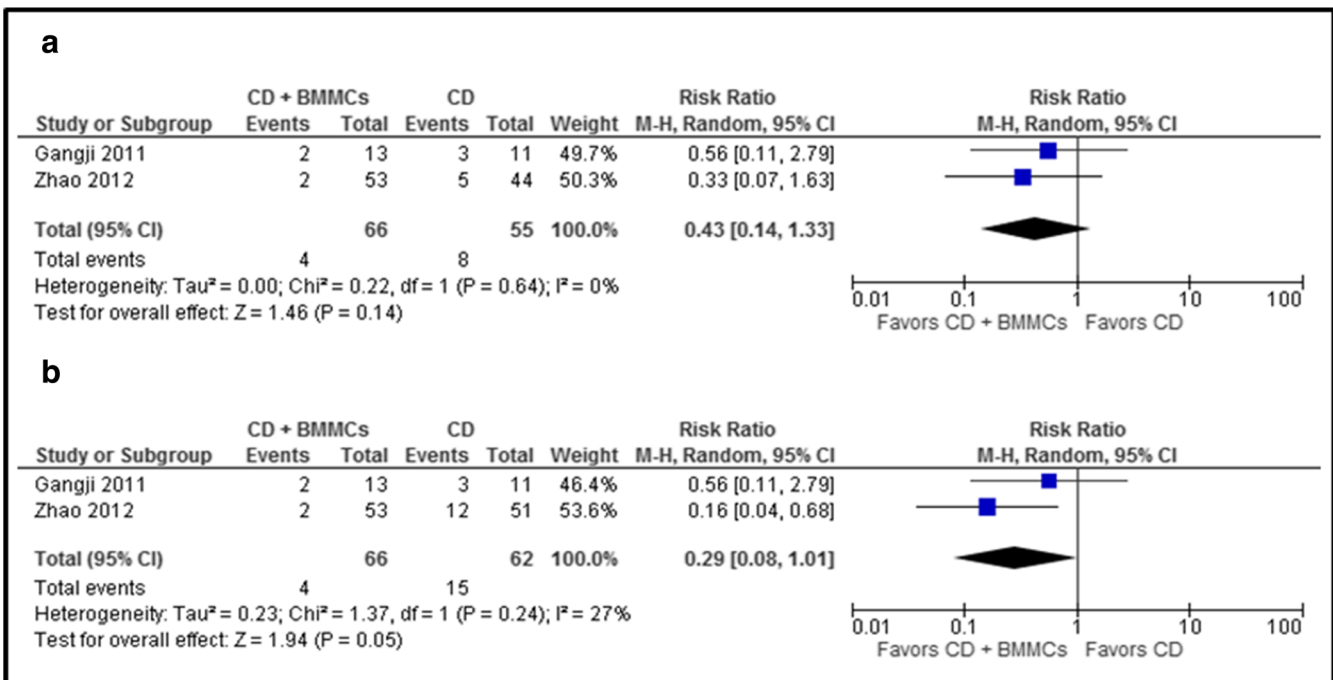


Fig. 5. a, b The graph shows the risk ratio for THR in CD with BMMCs versus CD alone. **a** Excluding hips lost to follow-up or excluded from analysis. **b** Assuming that all hips lost to follow-up or hips excluded from analysis underwent THR (worst-case scenario).

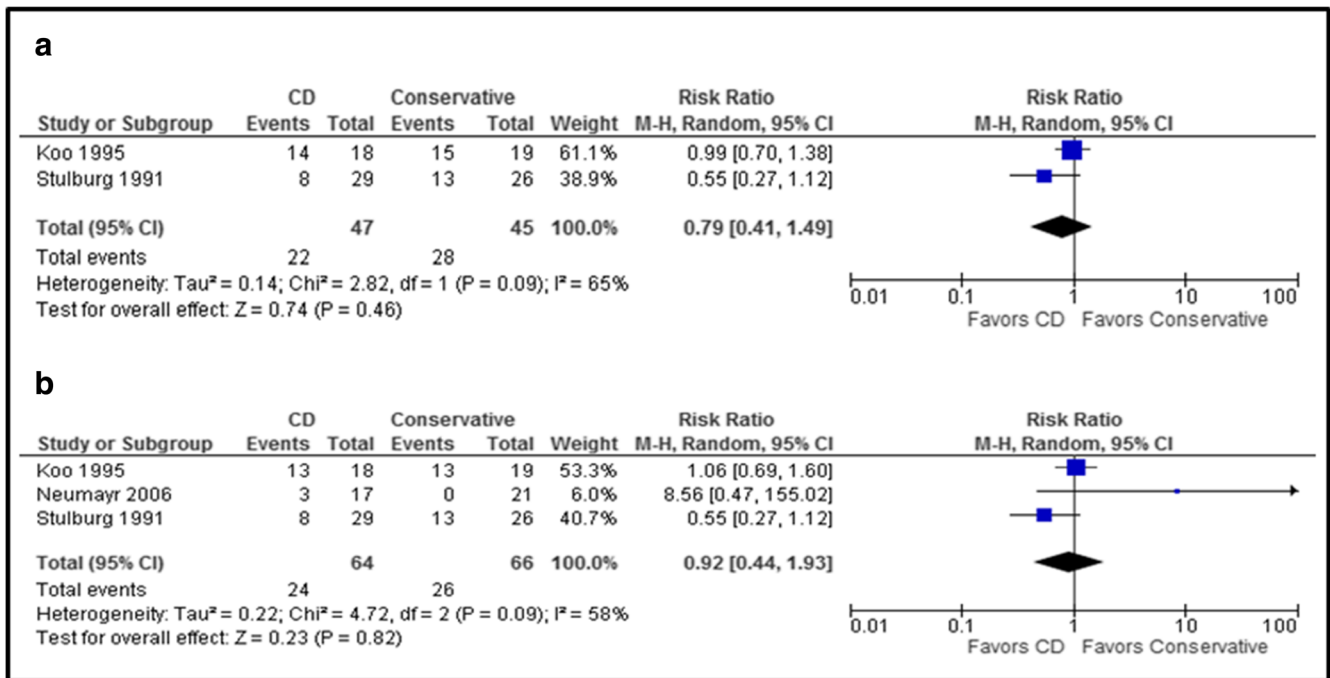


Fig. 6. **a, b** The upper graph (a) shows the risk ratio for femoral head collapse for CD versus conservative treatment. The lower graph (b) shows the risk ratio for THR in comparing CD versus conservative treatment (no hips were lost to follow-up).

for 24 weeks, while zoledronate treatment is administered 5 mg intravenously annually [27]. Both studies [9, 27] included patients with large osteonecrosis lesions ($\geq 30\%$)

at high risk of collapse. Contrarily to what has been reported in a prospective comparative study by Nishii et al. [39], our results suggest that in large size lesions, substitution of the

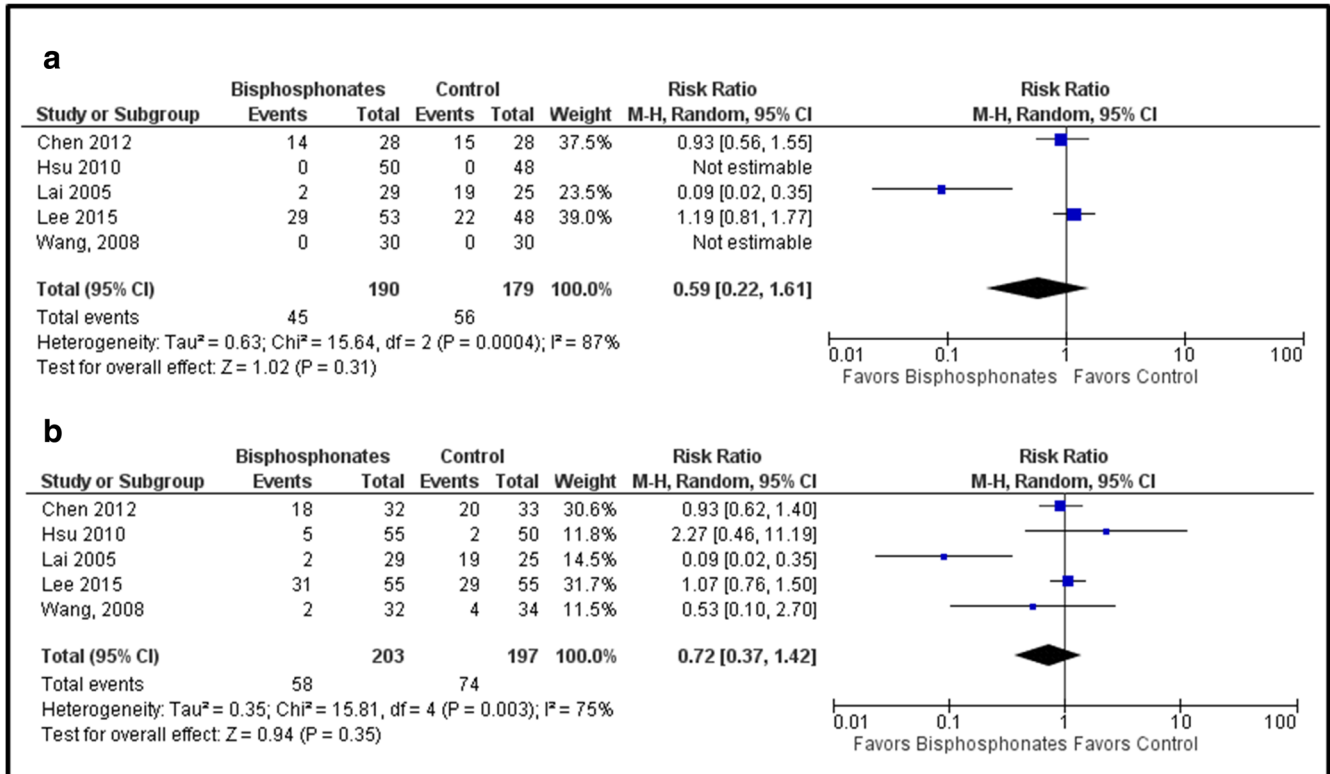


Fig. 7. **a, b** The graph shows the risk ratio for femoral head collapse when comparing bisphosphonates versus controls. **a** Excluding hips lost to follow-up or excluded from analysis. **b** Assuming that all hips lost to follow-up or hips excluded from analysis experienced femoral head collapse (worst-case scenario).

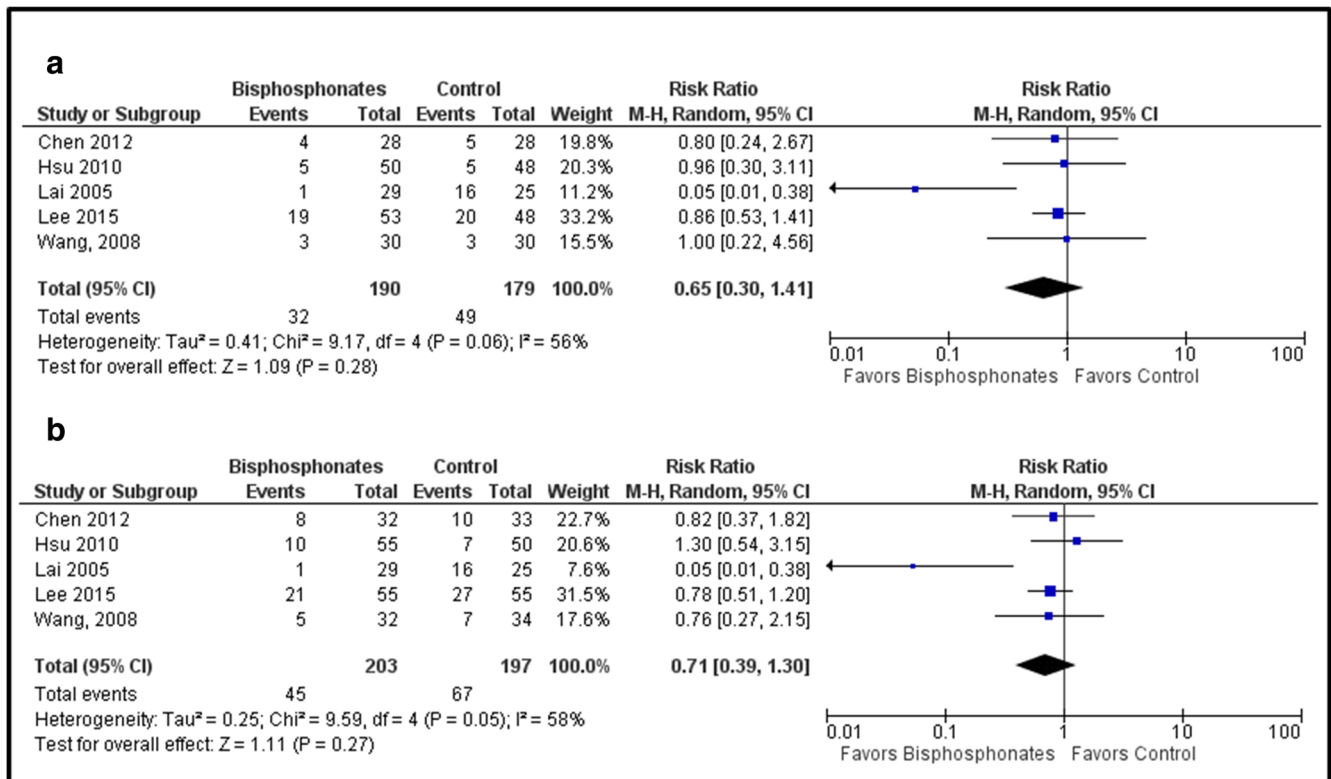


Fig. 8. a, b The graph shows the risk ratio for THR when comparing bisphosphonates versus controls. **a** Excluding hips lost to follow-up or excluded from analysis. **b** Assuming that all hips lost to follow-up or hips excluded from analysis underwent THR (worst-case scenario).

necrotic bone cannot be enhanced by bisphosphonate treatment alone. As shown in previous reviews, there is a lack of controlled and double-blind studies about the efficacy of bisphosphonates in the treatment of ONFH [8, 30]. However, noncontrolled studies appeared to demonstrate favorable results, particularly in diminishing pain, improving mobility, and lowering the incidence of collapse [8]. The controversy over the effectiveness of bisphosphonate use justifies the necessity for further research in this area. Outcomes of biophysical treatments were not analyzed in this study. ESWT groups were used as controls to compare the efficacy of alendronate in the treatment of ONFH [18, 51].

With regard to combining bisphosphonates and CD, Kang et al. [23] found that multiple drilling plus alendronate can delay the progression of ONFH and improve HSS scores when compared with multiple drilling alone at 4-year follow-up. These results suggest that combination of these two

treatments enhances their efficacy. CD improves vascularity by decreasing intra-osseous pressure [23]. Probably, the increase in blood flow to the femoral head also increases the amount of bisphosphonate reaching the area between the viable and the necrotic bone where osteoclast inhibition prevents the weakening of the cancellous bone [26, 27]. A previous review by Ma et al., however, does not recommend any adjunctive therapy (bisphosphonates, ESWT, iloprost, etc.) because studies combining adjunctive therapies and CD are limited by sample size, questionable efficacy, and low-level evidence [30]. It is to the authors’ belief that further RCTs are necessary on this topic. Studies using zoledronate are of interest since this nitrogen-bound bisphosphonate has the highest potency and affinity to the bone [23]. We also suggest more studies in large-size osteonecrosis lesions since it is known that small-size lesion will not progress without any intervention [13, 25, 36].

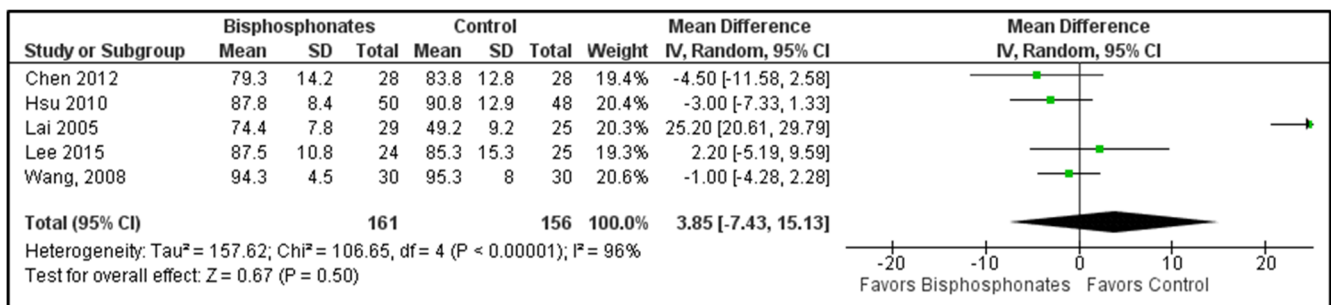


Fig. 9. Analysis for mean difference in follow-up HHS score when comparing bisphosphonates versus control.

Several limitations are present in this study. Limitations related with the included studies are the heterogeneity of study population in terms of risk factors, lesion size and stage, bilateral versus unilateral disease, surgical techniques, indications for THR, and follow-up time. Furthermore, included studies reported different classification systems (X-ray based and MRI based) decreasing the reliability to assess the status of avascular necrosis. Just three of the included studies reported ARCO classification, accounting for lesion location and area of head involvement; further RCTs using ARCO classification are encouraged. Another limitation is the inadequate reporting with regard to definition of “failure,” lost to follow-up patients, hazard ratio, and 95% confidence interval, which was seen in some studies. Limitations of the analysis included small number of RCTs in each comparative group and the assumption that hips that were lost or excluded from the analysis had the worst outcome. The last factor may have influenced the results but was necessary to analyze the data due to the lack of reported hazard ratios. The variability in functional outcome assessments did not allow to determine whether CD plus BMMCs or CD alone improves functional outcomes in patients with ONFH.

In conclusion, the current literature has demonstrated that there is a decrease in the risk to femoral head collapse in patients with ONFH treated with CD combined with BMMCs when compared to CD alone; however, there is no robust evidence to determine the effect on functional outcomes. Neither CD nor bisphosphonate treatment showed improvement on radiologic or functional outcomes. This study shows that there is a lack of RCTs assessing treatments for femoral head AVN. New studies comparing treatments as a function of ONFH stage when treatment is started, describing lesion sizes and using standardized surgical techniques and outcome measures, are required.

Compliance with Ethical Standards

Conflict of Interest: Jordan C. Villa, MD, Solomon Husain, BS, Jelle P. van der List, MD, Arianna Gianakos, DO, have declared that they have no conflict of interest. Joseph M. Lane, MD, reports other from Agnovos, Amgen, Bone Therapeutics, SA, Merck, Inc. CollPlant, Inc., Graftys, Kuros, and Lilly, Inc., outside the work.

Human/Animal Rights: This article does not contain any studies with human or animal subjects performed by the any of the authors.

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