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# Evidence for Using Alendronate to Treat Adult Avascular Necrosis of the Femoral Head: A Systematic Review

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Osteonecrosis or avascular osteonecrosis (AVN) of the femoral head is a devastating multifactorial disease that affects 20 000 persons each year in the United States. The purpose of this systematic review was to determine the efficacy and safety of alendronate for adult AVN during short- and long-term follow-up. Electronic databases were searched for randomized or nonrandomized clinical trials, cohort, case-control studies, and series of cases in which alendronate was used for treatment of adult AVN of the femoral head. Relevant articles with adequate data on reduction of pain, improvement of articular function, slowing of bone collapse progression, or need for total hip arthroplasty (THA) were included after applying inclusion and exclusion criteria. Eight articles involving 788 hips with evidence level 1b to 3b were included in this systematic review. Most studies suggested a positive short-term efficacy of alendronate treatment in reducing pain, improving articular function, slowing of bone collapse progression, and delaying the need for THA for adult AVN patients. The favorable long-term results were also presented in those treated patients after 10-year follow-up. In addition, there were no severe adverse effects associated with alendronate treatment observed during short- and long-term follow-up, and most of the included studies suggested use of alendronate in early AVN with small necrotic lesion to achieve better outcomes. The findings support consideration of alendronate use for adult AVN, particularly with early stage and small necrotic size. The lack of large-scale, randomized, and double-blind studies justifies new studies to demonstrate the detailed indication and the optimized strategy of alendronate treatment. Level of evidence: Level 3a.

**MeSH Keywords:** **Alendronate • Femur Head Necrosis • Review Literature as Topic**

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## Background

Osteonecrosis or avascular osteonecrosis (AVN) of the femoral head is a devastating multifactorial disease that affects 20 000 persons each year in the United States [1,2]. Although the pathophysiology of AVN has not been completely elucidated, this progressive clinical condition is characterized by bone death and reduced local blood flow [3]. As bone repair occurs, the imbalance of osteoclast-mediated resorption and delayed new bone formation result in mechanically weak bone that collapses under the load of weight [4]. After collapse, due to extreme pain and loss of hip function, most patients require standard total hip arthroplasty (THA) [5,6]. However, because of the young age of many of these patients, a hip replacement cannot be expected to last the patient's lifetime; therefore, when feasible, attempts should be made to save the femoral head prior to collapse with use of less invasive treatment modalities [7–9].

Identifying such conservative treatment options with potential benefits is extremely desirable. There is currently no uniformly accepted pharmacologic treatment that retards AVN progression and prevents bone collapse. In contrast to other drugs, bisphosphonates (Bps) are potent anti-reabsorptive agents that act by inhibiting the action of mature osteoclasts in the bone, which theoretically normalizes the uncoupled bone remodeling, contributing to femoral head collapse [10]. In the last decade, many studies have investigated the application of Bps in the treatment of AVN [10–19]. Nevertheless, the lack of controlled and long-term results, the substantial heterogeneities of genres in Bps, the unclear indication of various stages of AVN, and the combination of adults and juveniles, complicate the interpretation of recent systematic reviews [10,11] and necessitate new evidence.

Of different Bps, alendronate is the most widely prescribed and evident one. In addition, application of Bps in children raises great concern due to its potential harmful effects on the growing skeleton of juveniles. Therefore, we performed a systematic review restricted to alendronate therapy for adult AVN. By summarizing recent randomized controlled trials and long-term follow-up studies, the purpose of this systematic review was to determine the efficacy and safety of alendronate for adult AVN during short- and long-term follow-up. Our hypothesis was that alendronate therapy could be well-tolerated and: 1) improve clinical function and pain, 2) retard the progression of femoral head collapse and/or reduce the incidence of THA, and 3) be influenced by stage of the disease.

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Four electronic databases (PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure) were searched using a search strategy combining the terms in Boolean logic: “(alendronate OR

Fosamax) AND (avascular necrosis OR aseptic necrosis OR osteonecrosis) AND (femoral head)”. There was no limitation on language, year of publication, or publication status. Trials were included if they were randomized or nonrandomized clinical trials, cohort, case-control studies, and series of cases in which alendronate was used for treatment of AVN of the femoral head in adults, with adequately reported data on diminishment of pain, or improvement of articular function, or retardation of bone collapse progression, or need for arthroplasty. We also manually searched reference lists of review articles, and included studies to identify other potentially eligible studies. After exclusion of duplicates, 1 reviewer (LRB) performed an initial title and abstract screening of articles to discard those that were clearly ineligible, then 2 reviewers (LT and ZHM) independently examined the full article to assess the trials for eligibility for inclusion, with disagreements resolved by discussion. Citations were excluded if they were animal studies or targeted adolescences or used alendronate in combination with any other treatments. If necessary, we attempted to contact the author of the original report to obtain further details.

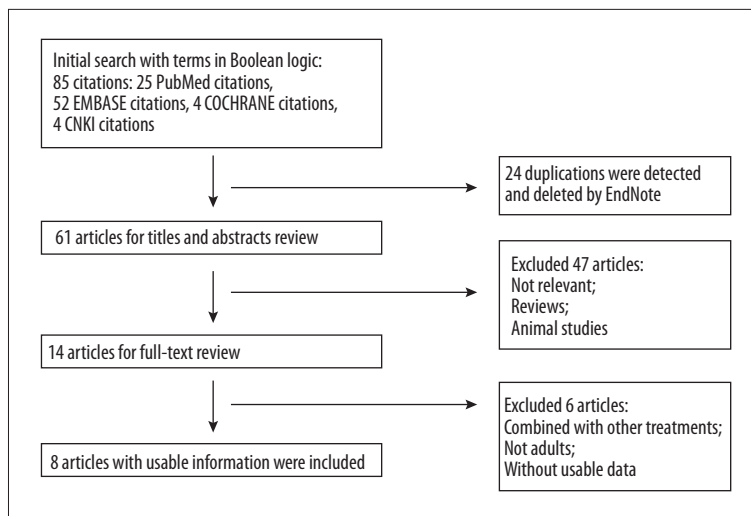
From each article we extracted the following details by using standardized forms: authors, year of publication, geographical location of study, study design/level of evidence, study population (hips/patients), patient sex and age, follow-up duration, interventions, outcomes, and adverse events.

The level of evidence of each study was rated on basis of *Oxford Centre for Evidence-based Medicine – Levels of Evidence* (March 2009) [20].

The outcome of interest included clinic function and hip pain improvement of AVN patients after alendronate treatment. The other relevant outcomes were clinical failure and radiographic failure rate of treated AVN. Clinical failure was defined as the need for THA. For the radiographic evaluation, although various classification systems were used among the studies, they shared fundamental similarities; therefore, radiographic failure here were defined as any lesions progressed to a higher stage from baseline stage [7,21]. Due to the included AVN comprising both pre-collapse and early-collapse stage, collapse rates were separated and considered as a new occurrence of collapse or an increased collapse of greater than 2 mm. Data could not be analyzed using a meta-analysis due to the methodological heterogeneity and limited number of the available controlled studies.

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Figure 1 details study identification, inclusion, and exclusion. Our search strategy initially yielded 85 citations. Of these, we included 8 articles with 788 hips in this systematic review [12–19]. Tables 1 and 2 show the characteristics of the included articles. All the studies were conducted in Asia and



**Figure 1.** A flow diagram demonstrates the method of article selection for clinical study inclusion.

published after 2000. All the studies targeted adult AVN patients within stage III classified by X-ray, magnetic resonance imaging (MRI), both according to Ficat and Arlet (3 studies) [13,14,17], Association Research Circulation Osseous (ARCO, 2 studies) [15,19], or Steinberg (University of Pennsylvania system, 2 studies) [12,16]. Four studies were restricted to non-traumatic AVN patients [12,15,16,19] and the other 4 articles from the same group did not specify the etiology [13,14,17,18]. The doses and duration of alendronate administration differed among the studies. In 5 of the included studies, patients were given calcium and vitamin D supplementation [12–14,17,18]. Full weight-bearing was only permitted in 1 study [15] and 4 studies only allowed partial or no weight-bearing [13,14,17,18]. Six studies reported short-term results of alendronate treatment on AVN (<4 years) [12,15–19], and the other 2 reported long-term results (≥4 years) [13,14].

Only 3 studies contained a control group [12,15,16], 2 of which were randomized controlled trials [12,16] that reported the details of randomization and blinding. Most of the included studies were prospective non-controlled studies and 4 of them were from the same institution reporting on the same group during different follow-up period [13,14,17,18].

As presented in Table 1, the level of evidence for the studies ranged from 1b to 3b. The current evidence is Level 3a, which is limited to the small number with small sample size and the majority of non-controlled studies [20].

Table 2 showed the outcomes reported from studies evaluating alendronate use in avascular osteonecrosis of the femoral head.

### Short-term outcomes analysis

Agarwala et al. [18] studied 16 patients with AVN of the femoral head – most of them secondary to the use of corticosteroids.

They used a regimen of alendronate 10 mg/day + calcium 1 g/day + vitamin D supplement, and the mean duration of therapy with alendronate was 24.7 weeks. Patients that used alendronate had a significant improvement in pain as early as 12 weeks, with a reduction in the need for analgesics and improvement in functional capacity in all patients, and this improvement was maintained for 24 weeks. The observation was extended to a total of 60 patients (100 hips), with an average follow-up of 37 months [17]. Alendronate was used in daily doses of 10 mg or weekly doses of 70 mg; these authors confirmed these findings and further suggested that alendronate would retard the progression of AVN and avoid the early indication of surgery in mid-term follow-up [17].

Another study with short-term follow-up was performed by Chen et al., which included 83 patients with non-traumatic AVN of the femoral head [19] – 33 of the patients were ARCO I and the rest were ARCO II. They were given oral alendronate 70 mg weekly, and evaluated with Harris criteria at baseline and 3 months after treatment. In the patients with ARCO I AVN, the scores of pain and function were improved after treatment ( $P < 0.01$ ). Similarly, in the patients with ARCO II AVN the scores of pain and function were both improved after treatment ( $p < 0.01$ ). And the score of activity was also enhanced obviously, which was not observed in ARCO I AVN patients. They concluded that alendronate is effective in treatment of early-stage adult non-traumatic AVN of the femoral head, especially for ARCO II patients.

The first RCT with short-term results evaluating the treatment of alendronate on AVN of the femoral head was by Lai et al. [16]. They studied 40 patients with Steinberg Stage II or III C non-traumatic AVN of the femoral head. The patients were divided into 2 groups, half of them received alendronate 70 mg/week orally and the other half did not receive this medication. The patients were monitored radiologically every 10 weeks and observed for a minimum of 24 months. At the end of the study,

**Table 1.** Demographics for included trials evaluating alendronate use in avascular necrosis femoral head

Author/ year/ area	Design/ level of evidence*	Number of hips/ patients (alendronate; control)	Gender (F/M)	Average age (year, alendronate; control)	Percentage of alcohol or steroid induced	Etiology of AVN	Detection of AVN	Stage of AVN (alendronate; control)	Follow-up time	Follow up rate
Agarwala/ 2002/ India	Open label, prospective, non- controlled study/ 3b	18/18	9/9	34 (19-44)	NA	NA	X-Ray and MRI	NA	24 weeks	100%
Agarwala/ 2005/ India	Open label, prospective, non- controlled study/ 3b	71/41	18/42	18-70	NA	NA	X-Ray and MRI	Ficat I (n=15); II (n=19); III (n=19)	37 months	1 year (71%); 2 year (42%); 2+ year (37%)
Agarwala/ 2009/ India	Open label, prospective, non- controlled study/ 3b	395/294	92/202	39.1 (22-55)	NA	NA	X-Ray and MRI	Ficat I (n=215); II (n=129); III (n=51)	4 years	92%
Agarwala/ 2011/ India	Open label, prospective, non- controlled study/ 3b	53/40	21/32	41.8±9	NA	NA	X-Ray and MRI	Ficat I (n=15); II (n=19); III (n=19)	10 years	63%
Chen/ 2011/ China	Open label, prospective, non- controlled study/ 3b	99/83	56/27	26-63	NA	Non- traumatic	X-Ray and MRI	ARCO: Stage I (33); II (50)	3 months	100%
Lai/ 2005/ Taiwan	Randomized, single-blind, placebo- controlled study /2b	29/20; 25/20	5/15; 5/15	42.6 (22-65); 42.4 ( 20-64)	59.09	Non- traumatic	X-Ray and MRI	Upenn Stage II (13; 12); III (12; 2)	24-28 months	100%
Nishii/ 2006/ Japan	Open label prospective comparative study /2b	20/14; 13/8	7/7; 7/1	48 (29-75); 36 (18-54)	93.94	Non- traumatic	MRI	ARCO: Stage I (10;4); II (5; 3); III (5;6)	1 years	88%
Chen/ 2012/ Taiwan	Multicenter, randomized, double-blind, placebo- controlled study /1b	32/26; 33/26	4/22; 7/19	48.4±11.4; 44.2±9.2	75.00	Non- traumatic	MRI	Upenn Stage IIC (20; 25); IIIC (12; 8)	2 years	81%

AVN – avascular necrosis; MRI – magnetic resonance imaging; Ficat – ficat and arlet; ARCO – Association Research Circulation Osseous; Upenn – University of pennsylvania system (Steinberg); NA – not available. \* The level of evidence was rated on basis of Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009).

the mean HHS was 49.2±9.2 points in the control group and 74.4±7.8 points in the alendronate group. It was also demonstrated that only 2/29 femoral heads with AN (0/17 in Stage II, 2/12 in Stage III) collapsed in the group that received alendronate 70 mg/week, whereas in the group that was randomized to not receive this medication, collapse occurred in 19/25

(9/13 in Stage II, 10/12 in Stage III) femoral heads (p<0.001). One hip in the alendronate group underwent THA, whereas 16 hips in the control group underwent THA (p<0.001). Thus, they concluded that alendronate appeared to prevent early collapse of the femoral head in the hips with Steinberg Stage II or III C non-traumatic AVN.

In a study by Nishii et al. [15], 14 patients (20 hips) with ARCO I–III AVN received alendronate 5 mg/day and were compared in a nonrandomized manner with a group of 8 patients (13 hips) that did not receive alendronate. No patient used walking assistance such as crutches or canes during the study. All the patients received periodical radiologic evaluation at 3, 6, and 12 months. At the end of follow-up, the group of patients receiving alendronate had less pain and a lower frequency of femoral head collapse when compared with the control group. Specifically, they found progressive collapse occurred only in hips with extensive necrosis (greater than the medial 2/3 of the weight-bearing area of the femoral head with/without involvement of acetabula edge, termed Type C2 and C1, respectively) in both groups, which had a much higher incidence in the control groups. In total, collapse occurred in 6/13 of articulations in the control group and in only 1/20 in the alendronate group ( $p=0.008$ ). Moreover, 2 of 13 hips in the control group needed THA, but none of patients needed surgery in the alendronate group.

Therefore they suggested alendronate had the potential to prevent collapse of the femoral head, even with extensive necrosis, within 1 year.

Chen et al. recently performed a 2-year, multicenter, prospective, randomized, double-blind study involving a total of 52 patients (65 hips) [12]. All patients presented with Steinberg Stage IIC or Stage IIIC osteonecrosis. Twenty-six patients (32 hips) were assigned to a scheme of alendronate 70 mg/week for 104 weeks and were compared with a group of 26 patients (33 hips) that received placebo. At the end of the study, MRI evaluation revealed that 21 of the 32 hips in the alendronate group and 20 of the 33 hips in the placebo group had progressed ( $P=0.636$ ). Four of 32 hips in the alendronate treatment group underwent THA, and 5 of 33 hips in the placebo group had THA ( $P=0.837$ ). No differences were noted in HHS, or Short Form 36 scores between the 2 groups. Thus, the extensive lesion of necrotic area might impair the prognosis of the AVN when alendronate was used.

**Table 2.** Methodology and outcomes reported from studies evaluating alendronate use in avascular necrosis of femoral head.

Author/Year/Area	Dose/average duration of treatment	Calcium or vitamin D3	Additional treatment	Timing of treatment initiation	Follow-up time	Adverse effects (n)
Agarwala/2002/India	10 mg per day a calcium 1 g per day for 24 weeks	1000 mg calcium and vitamin D3	Weight bearing was not permitted	NA	24 weeks	NA
Agarwala/2005/India	10 mg per day/70 mg per week during study period	500–1000 mg calcium and 400–800 IU vitamin D3	Non-weight-bearing	0–36 months after diagnosis	37 months	NA
Agarwala/2009/India	10 mg per day for 3 years	500–1000 mg calcium and 400–800 IU vitamin D3	Partial weight bearing, then increased gradually as dictated by pain	12.4 months after onset of hip pain	4 years	Dyspeptic symptoms: 10; headache and dizziness: 6
Agarwala/2011/India	10 mg per day for 3 years	500 mg calcium and 400 IU vitamin D	Partial weight bearing, then increased gradually as dictated by pain	7.4 months after onset of hip pain	10 years	Muscle pain and dizziness: 7
Chen/2011/China*	70 mg per week	NA	NA	Within 1 year after diagnosis	3 months	Abdominal discomfort :2
Lai/2005/Taiwan	70 mg per week for 25 weeks	NA	NA	NA	24–28 months	NA
Nishii/2006/Japan	5 mg per day for 1 years	NA	Full weight bearing	Within 4 years after diagnosis	1 year	Allergy and abdominal discomfort: 2
Chen/2012/Taiwan	70 mg per week for 104 weeks	500 mg calcium and 400 IU vitamin D in both groups	NA	Aln: 0.9±0.9 months; placebo: 2.0±2.9 months after diagnosis	2 years	None

**Table 2 continued.** Methodology and outcomes reported from studies evaluating alendronate use in avascular necrosis of femoral head.

Author/ Year/Area	Clinical function		Hip pain		Radiologic failure rate**		Clinical failure rate***
	Baseline	After treatment	Baseline	After treatment	Progression	Collapse	
Agarwala/ 2002/India	NA	Significant improvement in disability	VAS: 6.9 ( 3–10 )	Aln: 6 wk 4.9 (1–6); 12 wk 3.8 (1–7); 24 wk 3 (1–7)	Aln: 6.3% (1/16)	NA	NA
Agarwala/ 2005/India	NA	Significant improvement in disability, walking and standing time	VAS: 6.0±2.4	Aln: 1 yr (2.2±1.8); 2 yr (1.6±1.5); 2+ yr (2.0±2.0)	Aln: 1 yr (13%, 10/79); 2 yr (29%, 12/42); 2+ yr (54%, 20/37)	NA	THA: 1 yr (5/79); 2 yr (10/55); 2+ yr (10/50)
Agarwala/ 2009/India	NA	Significant improvement in clinical outcomes other than Stage III	VAS: Stage I (4.5±1.8); II (5.1±1.7); III (4.9±1.7)	VAS: Stage I (1.8±1.8); II (3.0±2.1); III (7.0±1.7)	Aln: Stage I: 46% (99/215); II: 54% (70/129); III: 20% (10/51)	Aln: Stage I-II: 12.6% (27/215); III: 55.8% (72/129)	THA: Stage I: 2% (4/215); II: 8% (10/129); III: 33% (17/51)
Agarwala/ 2011/India	NA	Worsening after stopping treatment	Median VAS: 8	Median VAS: Stage I (4.5); II (6); III (4)	Aln: Stage I: 38% (20/53); II: 33% (5/15); III: 37% (7/19); III: 42% (8/19)	Aln: Stage I: 29% (10/34); II: 20% (3/15); III: 37% (7/19)	THA: Aln: Stage I: 13.2% (7/53); II: 7% (1/15); III: 5% (1/19); III: 26% (5/19)
Chen/ 2011/China*	HHS: I: 91.03; II: 87.14	HHS: I: 95.21; II: 91.86	HHS: Pain: I: 38.45±5.55; II: 37.62±6.65	HHS: Pain: I: 41.45±3.55; II: 40.40±4.31	NA	NA	NA
Lai/ 2005/Taiwan	HHS: Aln: 67.6 (26–88); control: 65.7 (34–84)	HHS: Aln: 74.4±7.8; control: 49.2±9.2	NA	NA	Aln: Stage I: 13.7% (4/29); II (12%, 2/17); III ( 17%, 2/12); control: 80% (20/25). Stage II (77%, 10/13); III ( 83%, 10/12)	Aln: Stage II ( 0%, 0/17); III (17%, 2/12). control: 76% (19/25). Stage II (69%, 9/13); III ( 83%, 10/12)	THA: Aln: 3% (1/29); control: 64% (16/25)
Nishii/ 2006/Japan	NA	NA	NA	Aln vs. Control unchanged: 15 vs. 6, improved: 4 vs. 0, worsened: 1 vs. 7 (p=0.003)	Aln: 6.7% ( 1/15); control: 46.2% (6/13)	Aln: A-C1: 0/15; C2: 20% ( 1/5); control: C1 43% (3/7); C2: 75% (3/4)	THA: Aln: 0/15; control: 15.4% (2/13)
Chen/ 2012/Taiwan	HHS: Aln: 78.1±12.5; control: 76.6±15.2 (p>0.05)	HHS: Aln: 83.8±12.8 (p>0.05)	NA	NA	Aln: 65.6% (21/32); control: 60.6 (20/33)	Aln: 31% (10/32); control: 27% (9/33)	THA: Aln: 12.5% (4/32); control: 15.2% (5/33)

Aln – alendronate; HHS – Harris hip score; VAS – visual analog scale; THA – total hip arthroplasty; NA – not available. \* This article was published in Chinese and the pain data presented the from Harris hip scores, the higher of which indicated better pain improvement. \*\* The radiographic failure was determined as any lesions progressed from a lower stage to a higher stage and collapse rate was determined as a new occurrence of collapse or an increased collapse of greater than 2 mm. \*\*\* The clinical failure was defined as the need for total hip arthroplasty.

### Long-term outcomes analysis

The long-term data was from a study by Agarwala et al., who presented a clinic radiological analysis of 395 hips with a mean follow-up of 4 years [14] and then further extended the follow-up of 40 patients (53 hips) with AVN to 10 years [13]; those patients were treated with oral alendronate for 3 years, and the data demonstrated although clinical functions showed a general trend of worsening after discontinuation, patients tolerated the decline well, as suggested by the reduction in pain of Ficat and Arlet Stage I–III patients 10 years after onset of alendronate treatment. More importantly, the rates of radiologic progression and femoral head collapse were markedly reduced even at 10 years as compared to the historical data available for natural history of hips with untreated AVN. At 10 years, 46 (87%) of the 53 hips survived, that is, had a satisfactory clinical result. Hip loss to arthroplasty occurred in 1 each of Stage I (7%) and Stage II (5%) hips and in 5 (26%) of Stage III hips. Of the 34 hips that were in pre-collapse stages at the onset of the study, at 10 years 10 had collapsed, indicating a collapse rate of 29% for a period of 10 years. Mean time to collapse was 4.2 years. They thereafter indicated that the benefit is particularly marked if the treatment is begun in the pre-collapse stages of the disease (Stage I or II). Even in Stage III hips some benefit was obtained from treatment with alendronate by at least a delay in the need for total hip replacement [13].

### Adverse events analysis

None of the studies noted serious adverse effects related to alendronate administration. The most common adverse effects across the studies were gastric dyspepsia mentioned in 3 studies [14,15,19] and dizziness mentioned in 2 studies [13,14], both of which occurred after treatment initiation and were self-limiting. No osteonecrosis of the jaw were seen irrespective of the dose or duration of alendronate.

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Many surgical procedures have been described for preventing femoral collapse and progression of AVN. The most studied is core decompression, which works by reduction of intramedullary pressure inside the femoral head by making a drill hole, thus improving blood flow to bone. This procedure is mainly indicated in early-stage AVN [22]. Osteotomy could relocate the necrotic area of bone from the weight-loading area of the acetabulum, so as to redistribute the weight loading to articular cartilage, which is supported by healthy bone [23]. The increasingly applied method is bone graft, aiming to provide mechanical support to subchondral bone or cartilage. There are various types of bone grafting, some combined with osteotomy, osteochondral grafts, muscle pedicle bone grafts, and some are vascularized grafts

to improve blood flow of the bone by achieving revascularization [24,25]. The new tantalum rod is made of a biocompatible material with 75% porosity. It has been used to replace the necrotic bone segment to prevent collapse in Steinberg Stage I–III femoral AVN. The presence of pores allows rapid bony ingrowth [26]. However, the efficacy and safety of the above procedures are still controversial [7,27–29]. Due to the reported efficacy of total hip arthroplasty and the typical age of patients with osteonecrosis, it has recently been questioned whether these invasive procedures are appropriate, given the potential difficulty of later conversion to a hip replacement [7,30].

Conservative treatment that helps improve function and delays femoral head deformity could be valuable time-buying strategy for some patients. Some of the pharmacologic agents that have been used to treat osteonecrosis of the hip are statins [31,32], anticoagulants [33,34], prostacyclin [35,36], and Bps [10–19]. The theoretical benefit of statins is based on the association of increased fat cell size with an increased risk of development of hip osteonecrosis [37,38]. Anticoagulants may inhibit the aggregation of platelets and enhance blood flow to ischemic areas of bone [34]. Prostacyclin may promote bone regeneration on a cellular or systemic level [35].

However, collapse of the femoral head appears to be a consequence of the non-coupling of bone reabsorption and bone regeneration rates. In this context, collapse could be prevented if the reabsorptive activity of the necrotic bone during the repair phase was inhibited or slowed until the formation of sufficient new bone [10]. This is the characteristic rationale for use of alendronate in AVN.

The efficacy of alendronate therapy of femoral head deformity was indicated by several experimental studies consisting of both adult rat and rabbit models induced by femoral head ischemia. In 2 closely related studies, alendronate given subcutaneously (200 mg/kg/d) was able to preserve femoral head structure in mature rats during a 6-week follow-up [39,40]. In another study [41], 3-week alendronate therapy reduced degeneration of articular cartilage and improved subchondral bone volume and mineral density in adult rabbits at 12 months, which therefore might be the reason that alendronate treatment could preserve the shape of the femoral head affected by AVN.

Regarding alendronate for the treatment of AVN in clinical trials, in the present review, only 8 articles were published. Our literature search found were 2 recent systematic reviews evaluating BPs for AVN, 1 of which only included 3 observational short-term studies in juveniles [10], and the other with 6 small short-term trials that reported substantial heterogeneities across studies in patient group (adults and adolescents) and treatments (other BPs and combined therapy) [11].

In contrast to previous reviews, the inclusion criteria of the current review were restricted to articles that studied alendronate treatment for adult AVN. We only analyzed alendronate because it was the most widely studied BPs for AVN. Due to ongoing debate on long-term effects of alendronate on the growing skeleton, we limited the studied population to only adults. The inclusion of most recent longer-term results and RCT would also help to update the previous evidence. Furthermore, after determining an overall profile of clinic outcome and the rates of radiographic and clinical failure, the collected data were further stratified by radiographic stage and by duration of follow-up to determine whether any of these factors influenced the results.

However, generally speaking, the studies included in the current review still present various limitations – most used observational non-controlled methods; small numbers of patients; different AVN stages of patients when treatment was initiated; and lack of uniformity in dose and time of alendronate use. These articles, in addition, had various durations of follow-up and were composed of various subgroups of patient populations [13,14].

Bearing in mind the above-mentioned limitations, most studies suggested a positive short-term and middle-term efficacy in pain reduction, improvement of articular function, slowing of bone collapse progression, and delaying the need for arthroplasty in adult AVN patients with the use of alendronate treatment. This is of great clinical significance, as most of the included patients are young or active patients who are likely to require a revision at some point in the future and the effective slowing of femoral head deformity by alendronate could help to avoid early THA. Favorable long-term results were also presented by Agarwala's 10-year study in treated patients even after alendronate discontinuation [13]. In addition, there were no severe adverse effects associated with

alendronate treatment observed during short- or long-term follow-up. Another finding of the current review is that although patients in all stages appeared to have potential benefit from alendronate treatment, the application in early AVN with small size lesion was suggested by most of the included studies. Specially, as shown in Chen's study, when extensive osteonecrosis (Stage II C and III C) were radiographically presented, alendronate did not have any benefits. Thus, the efficacy of alendronate for AVN with large necrotic lesions should be considered more carefully [12].

## Conclusions

Our findings support consideration of alendronate use for AVN in adults because short-term and long-term favorable results could be expected, particularly with the early stage and with small necrotic size. Nevertheless, the lack of large-scale, randomized, and double-blind studies should be noted, and future studies should be developed to demonstrate the following aspects. 1) The detailed indication of AVN for alendronate treatment should be further clarified; for example, what type of AVN, traumatic or non-traumatic, which stage of AVN, including what size and what location of the necrotic lesion should be preferentially indicated. 2) There are a number of patient-specific factors that must be considered, including age, comorbidities, life expectancy, health, and activity level. 3) We also need to optimize the strategy of treatment, including timing of treatment initiation and alendronate therapy dose and duration.

## Disclosures

All authors indicate they have no conflict of interest.

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