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Mini Review Article

The effects of biphosphonate use in the healing of hip fractures: A systematic review

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Abstract

Hip fractures are serious fractures in the upper quarter of the femur bone. The underlying cause of most of them is osteoporosis. Biphosphonates are the most commonly prescribed drugs used to treat osteoporosis worldwide. However, there are concerns as to whether their use can cause problems with the healing of hip fractures and if so, is the timing of their initiation and the duration of their application important? The purpose of this systematic review was to answer the above questions. A literature search was conducted, with the use of the PubMed, Google Scholar and Cochrane databases. The abstracts of all potentially relevant studies, were extensively examined. All of them referred to the biphosphonate treatment, the duration of healing and/or the non-union rates of hip fractures, were included to the study. Biphosphonates, were found to affect hip fracture healing, when applied prior to the fracture and to have no effect on healing process, when applied after the fracture event. There was no statistically significant correlation between treatment duration and union time. There is a need of additional studies to investigate the effects of biphosphonates on hip fracture healing. These studies need to be focused on healing time, non-union rates and the duration of treatment.

Keywords: Hip fracture, Biphosphonates, Union, Non-union, Fracture healing

Introduction

Hip fractures are serious fractures in the upper quarter of the femur bone. Their presence is related to the increase of age, with most cases occurring in people over 75 years old (y.o)[1]. Falling, poor vision, weight and height are all seen as risk factors. They are classified as intracapsular and extracapsular. In intracapsular hip fractures belong the fractures of the femoral head and those of the femoral neck (subcapital, transcervical and basicervical). In extracapsular hip fractures belong intertrochanteric and subtrochanteric fractures[2]. Their diagnosis is generally made by clinical examination and imaging tests[3]. Most of them are treated surgically by implanting anorthosis. Non-operative treatment is applied in very rare cases[1]. Hip fractures and hip surgery can lead to a large number of complications such as nonunion, malunion, avascular necrosis, wound infections, implant failure, deep venous thrombosis (DVT), pulmonary embolism, heart attack, stroke, chest and urinary tract infections and pressure sores on the sacrum and heels[4].

Patients with hip fractures are at high risk for future fractures including hip (mainly), wrist, shoulder and spine. The underlying cause of most of these fractures is osteoporosis, thus after treatment of the acute fracture, patients must receive work up and treatment for it. Current treatment standards include the starting of a biphosphonate. Biphosphonates are a class of drugs that prevent bone mass loss. They are the most commonly prescribed drugs used to treat osteoporosis worldwide[5]. Evidence shows that they reduce risk of fractures in postmenopausal women with osteoporosis[5-7]. They are accumulated in high concentration in bone (preferentially into sites with high turnover rates) due to their binding affinity to hydroxyapatite crystals, inhibiting crystal breakdown and suppressing bone resorption[8]. Of the biphosphonate that is resorbed (orally or intravenously), about 50% is excreted unchanged by kidney and the remainder is absorbed onto bone surface[5]. Long-term treatment with biphosphonates produces anti-fracture

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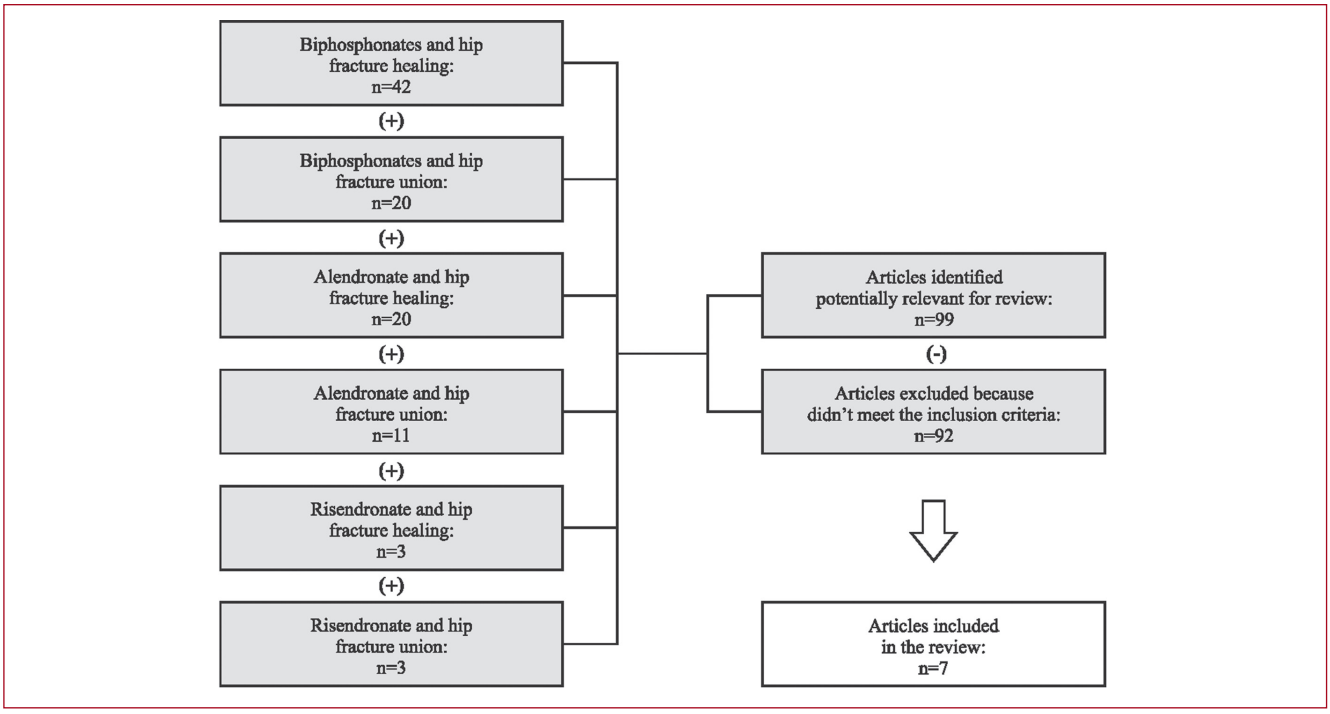

Figure 1. Selection process for articles.

and mineral density effects that persist for 3-5 years, after an initial 3-5 years of treatment[5]. After five years of medications by mouth or three years intravenously, among those of low risk, biphosphonate treatment can be stopped[9]. In those at higher risk, ten years of medications orally or six years intravenously may be used[9].

Generally, biphosphonates are drugs that are well tolerated by the vast majority of patients, and evidence shows that are relatively safe[10]. Adverse effects include gastritis, esophagitis, musculoskeletal pain and there are also recent studies that report them as a risk factor for atrial fibrillation in women[10-13]. Other reported complications are osteonecrosis of the jaw and atypical fragility fractures of the femoral shaft (diaphyseal or subtrochanteric) and neck[14-17]. However, there are concerns as to whether the use of bisphosphonates can cause problems with the healing of hip fractures and if so, is the timing of their initiation and the duration of their application important[15]? The purpose of this systematic review was to answer the above questions.

Literature search

A literature search was conducted during the first week of April of 2016, with the use of the PubMed, Google Scholar and Cochrane databases. The keywords that we used were: biphosphonates and hip fracture healing, biphosphonates and hip fracture union, alendronate and hip fracture healing, alendronate and hip fracture union, risendronate and hip fracture healing, risendronate and hip fracture union. All abstracts found with the aforementioned method, were examined whether they were relevant to the aim of this review. From the study were excluded articles that were not written in English, when the full text was not available and those with patients suffering from bone metastases, hip tumors, multiple myeloma and metabolic diseases other than osteoporosis. The articles that were included in the study, should be referred to treatment with bisphosphonates, to the duration of fracture healing and/or to the non-union rate of the fractures. Healing was defined radiologically, as bridging at the fracture site by a callus or a cortical continuity involving at least three cortices in the hip using anteroposterior and lateral views of the femur and clinically by the ability of the patient to fully bear weight and by the lack of pain at the fracture site[16].

Results

The literature research in PubMed, Google Scholar and Cochrane databases, with the above mentioned keywords, identified 99 potentially relevant articles. After an extensive examination of their abstracts, only seven of them were found to meet the inclusion criteria of the study and were retrieved for further evaluation. The references of these articles were also investigated for other relevant articles, in order to be included in the study. However, there weren't other that met the inclusion criteria of this review. Therefore, only the aforementioned seven articles were finally included (Figure 1).

ARTICLE	STUDY TYPE	LEVEL OF EVIDENCE	FOLLOW-UP TIME
Kim et al.	Prospective randomized case study	II	> 12 months
Lyles et al.	Randomized double blinded controlled trial	I	Median 1.9 years
Odvina et al.	Case series	IV	Up to 2 years
Das De et al.	Retrospective cohort study	III	Up to 60 months
Teo et al.	Retrospective cohort study	III	Mean 21.7 months (range 0-53)
Prasam et al.	Retrospective case control study	III	Mean 29 months (range 5-60)
Egol et al.	Retrospective cohort study/case study	III	Mean 33 months (range 6-85)

Table 1. Types of the studies included in the review.

ARTICLE	NUMBER OF PATIENTS	AGE (Years)	SEX (Male/Female)
Kim et al.	Group A: 26 Group B: 26 Group C: 25	Group A: 75.0 (SD 10.2) Group B: 75.3 (SD 9.9) Group C: 78.1 (SD 9.5)	Group A: 7/19 Group B: 10/16 Group C: 10/15
Lyles et al.	Total: 2127 Cases: 1065 Controls: 1062	Cases: 74.4 ± 9.48 Controls: 74.6 ± 9.86	Total: 508/1619 Cases: 248/817 Controls: 260/802
Odvina et al.	1	49.0	0/1
Das De et al.	Total: 20 Cases: 12 Controls: 8	63.1 (range 44-88)	1/19
Teo et al.	33	67.5 (range 47-91)	0/33
Prasam et al.	Total: 20 Cases: 12 Controls: 8	> 50	Cases: 0/12 Controls: 0/8
Egol et al.	19*	59.3 (range 46-75)	2/17**.

**19 patients with a total number of 25 subtrochanteric fractures, **5 of 17 female patients had bilateral fractures*

Table 2. Demographics of the patients.

There were four retrospective cohort studies, one randomized double blinded controlled trial, one prospective pilot study and one case series study. One of them was of evidence level 1, one of level 2, four of level 3 and one of level 4. The minimum follow-up time for all of the studies was 52 weeks (Table 1). The ethnicity of the patients was specified in two of the seven articles and their race in only one. Their number varied from 1 to 2127 and their mean number per study and was 328.1. Of them, 1759 (76.6%) were females and 511 (23.4%) males. Their age varied from 44 years old (y.o.) to 91 y.o. Despite the fact that in one study the age of the patients was not specified, it was mentioned that all of them were over 50 y.o. For the rest six studies, where the data about age were available, the mean of all the average ages was 64.9 y.o (Table 2). In four of the seven articles were reported co-morbidities such as hypertension, coronary artery disease, diabetes mellitus, previous stroke, osteoarthritis, depression, asthma, Adamantiadis-Behcet's disease, renal transplantation, tobacco and alcohol use.

The types of biphosphonates used and details about their dosage, were specified in four of the seven studies. In five studies the drug was applied before the hip fracture, for a mean time period of 5.8 years (range 3.0 -8.8 years). In the remaining two studies the biphosphonate was taken after the fracture. In one of these two, the mean duration of application was 3 years and in the other, the drug was applied for more than 1 year, in three different groups of patients according to the timing of its commencement. The types of hip fractures were specified in six studies (Table 3).

All of the fractures were treated surgically, using different operative techniques. Of the five articles, wherein the bisphosphonates had been applied prior to the fracture, only

ARTICLE	BIPHOSPHONATE TYPE	DURATION OF BIPHOSPHONATE	FRACTURE TYPE
Kim et al.	Risedronate 35 mg/week	Group A: 1 week postoperatively (p.o) * Group B: 4 weeks p.o* Group C: 12 weeks p.o*	Intertrochanteric
Lyles et al.	Zoledronic Acid i.v. within 90 days p.o. and every 12 months after	3 years p.o	Not specified
Odvina et al.	Alendronate 70 mg/week	3 years pre op.	Subtrochanteric
Das De et al.	Alendronate (12/20 patients), 70 mg/week	4.6 years pre op.	Subtrochanteric
Teo et al.	Not specified	4.9 years pre op.	Subtrochanteric
Prasam et al.	Not specified	Mean 7.6 years (SD: 3.4, range 1-12), preoperatively (pre op.)	Subtrochanteric
Egol et al.	Not specified	Mean 8.8 years (range 5-20), pre op.	Subtrochanteric

** Continued for ≥ 1 year after.*

Table 3. Biphosphonates and types of fractures.

ARTICLE	SURGICAL REPAIR	UNION TIME	DELAYED UNION	NON-UNIONS	IMPLANT FAILURES	REVISION SURGERIES
Kim et al.	IMN*/CHS‡ Group A: 17/9 Group B: 15/11 Group C: 15/10	Group A: mean 10.7 weeks (SD 4.4) Group B: mean 12.9 weeks (SD 6.2) Group C: mean 12.3 weeks (SD 7.1)	-	-	6	6 (Bipolar Hemiarthroplasty)
Lyles et al.	Not specified	Not specified	Incidence Cases: 34 (3.2%) Controls: 29 (2.7%) (risk ratio for Zoledronic Acid group: 1.17; 95 CI; 0.72 to 1.90; P=0.61)	-	-	-
Odvina et al.	Plate fixation & Bone graft	-	1 (2 years)	-	-	-
Das De et al.	IMN/EM‡ Cases: 6/6 Controls: 0/6	Not specified	-	Total: 3 Cases: 2 Controls: 1	1 (Cases)	1
Teo et al.	DCS¥: 10 DHS§: 8 Plate &Screws: 5 IMN: 10	10 months (2.2 to 27.5); ICC of 0.9; (95 CI; 0.91 to 0.98)	4	1	6	7
Prasam et al.	IMN & Plate fixation	Cases: mean 26 weeks Controls: mean 19 weeks	-	1	-	-
Egol et al.	IMN	Mean 8.3 months (2-18)	-	1	-	-

**IMN: Intramedullary nail, †CHS: Compression Hip Screw, ‡ Extramedullary Device, ¥ Dynamic Condylar Screw, § Dynamic Hip Screw.*

Table 4. Surgical repair, union time, delayed union, non-unions, implant failures, revision surgeries.

three presented the mean time of fracture union. In one of them, there were four cases of delayed fracture healing. Four of the five articles, reported the number of the non-unions and two, the cases that the implants failed. One of the two articles, wherein the biphosphonates were taken after the fracture event, was mentioned in the time of fracture union. The second one, reported only the incidence of delayed fracture healing (Table 4).

Discussion

Hip fractures are associated with increased morbidity, functional decline, and death in older adults, as well as increased use of health care services[17]. Mortality is increased in the year after the hip fracture, with reported rates of 15 to 25% and an estimated 9 excess deaths per 100 patients among women 70 years of age or older[18-26]. Falling from standing height is the most common risk factor (approximately 90% of hip fractures)[27]. A hip fracture following a fall is likely to be a pathological fracture. The most common causes of bone fragility are: osteoporosis, other metabolic bone diseases (Paget's disease, osteogenesis imperfecta, osteomalacia, osteopetrosis), primary bone tumors (benign or malignant), metastases, smoking, glucocorticoids, etc[28]. However, data suggest that few patients with hip fractures actually receive pharmacologic therapy for osteoporosis[29-31]. Biphosphonates are inhibitors of bone resorption by acting on osteoclastic activity[5]. They are the most commonly used medicaments in osteoporosis treatment. There are two types of biphosphonates: nitrogen containing and non-nitrogen containing. Both of them inhibit apoptosis of osteocytes and osteoblasts[32]. They are ingested by osteoclasts and they induce them to undergo apoptosis by two different methods. Nitrogen containing biphosphonates inhibit osteoclast farensyl pyrophosphate synthetase enzyme, required in mevalonate and in that way they inhibit GTPase formation. On the other hand, non-nitrogen containing biphosphonates form a toxic adenosine triphosphate (ATP) analogue, leading osteoclasts to premature death[33]. Although they are generally safe and effective, they carry the potential risk of over-suppressing bone turnover that can potentially impair some of the biochemical properties of bone. Treatment of patients with osteoporosis using biphosphonates during fracture healing is controversial because their conflicting anti-osteoclastic action. Osteoclasts are important for remodeling the callus into cortical bone, but biphosphonates inhibit osteoclast-mediated bone resorption in order to prevent bone loss and improve bone strength[34-36]. Several articles have addressed the effects of biphosphonates on animal fracture healing. In experimental animals, they have been shown to inhibit normal repair of micro-damage arising from marked suppression of bone turnover, which, in turn, results in accumulation of micro-damage and inhibiting fracture healing[37]. On the other hand, it has been shown that dogs treated with alendronate during the healing period had delayed callus remodeling, but that there was no adverse effect on the fracture healing[38-39]. A lot of studies have raised concerns about the action of biphosphonates on fracture healing in humans[40-41]. Rozental et al, compared 43 patients with a fracture of the distal radius, who were taking biphosphonate, with 153 controls and reported that time to union in the biphosphonate group was 55 days compared with 49 days in the control group[41]. Solomon et al, found increased relative risk of non-union of humerus fractures associated with biphosphonate use following the fracture[42]. However, despite the fact that a large number of patients who are receiving biphosphonates undergo hip fractures, relatively few studies have reported the effects of biphosphonate use on hip fracture healing[43-47,51-52].

The purpose of this study was to determine whether the use of bisphosphonates can cause problems in the healing of hip fractures, as well as the importance of the timing of their initiation and of the duration of their application. As mentioned before, the studies that were included in this review can be divided into two groups. The first group contains the studies where the patients were receiving biphosphonates prior to the hip fracture and the second one the studies where the patients received biphosphonates after the fracture event. Their results about the effects of biphosphonates in hip fracture healing differ. In the first group, all of the authors seem to agree that the use of biphosphonates can affect the healing process. Prasarn et al[43], compared their findings with the findings of similar hip fractures in patients that were not receiving biphosphonate therapy and they found that hip fractures associated with biphosphonate intake appeared delayed healing as well as a case of non-union. Egol et al[44], reported high rates of radiographic healing (98%), but a delay in healing time of hip fractures between patients who were receiving biphosphonates and those who were not. Das De et al[45], found a slightly higher incidence of non-unions, in patients who sustained subtrochanteric fractures and were using alendronate. Teo et al[46], observed that when using biphoshonates, hip fracture healing was slow and patients were subjected to a prolonged period of immobility. Finally Odvina et al[47], concluded that alendronate can result in poor healing in that kind of fractures. The findings of this review, for the first group of studies, agree with the results of other studies in the literature, about fracture healing in other body locations, where the biphosphonates were applied prior to the fracture[41,48-49]. However, a case-control study of femur fractures, conducted by Lin et al, showed a difference in the overall weighted mean union time, but difference was not statistically significant[50]. The above disagreement may be explained due to different types of fractures, and the different techniques and implants that were used. In our opinion, this discrepancy underlines the need for further research.

On the other hand, in the second group of studies, authors consider that the application of biphosphonates after a hip fracture, does not affect the healing process. Kim et al[51], found that the timing of biphosphonate therapy after an intertrochanteric fracture, didn't affect fracture healing or

the incidence of complications. Lyles et al[52], did not observe significant difference in delayed union of fractured bone, between a biphosphonate treatment group and a control study group. The above results are in agreement with the results of other similar studies, that investigated the effects of biphosphonate use after the fracture, in the healing of other fracture types[53-54].

In both groups of studies, there was no statistically significant correlation between duration of biphosphonate treatment and union time of hip fractures. This is in contrast with previous studies, for other kinds of fractures, who investigated the association between union and the duration of biphosphonate therapy. Armamento-Villareal et al[55], in their retrospective cohort study looking at low-energy cortical fractures, demonstrated significantly suppressed bone turnover on histological analyses in 15 patients who had consumed bisphosphonates for a mean of 5.7 years (range 2.0-10.0 years). Fourteen patients were exposed to alendronate, and one patient had taken risedronate. Fracture locations included shaft of the femur, rib, metatarsal, pelvis, fibula and ankle. The investigators found that in bone biopsies from patients with suppressed turnover (10 patients, 67 %), the mean bisphosphonate use was 6.5 years, whereas in bone biopsies from patients with normal bone turnover (five patients, 33 %), the mean bisphosphonate consumption was 3.9 years (p=0.02). The histology of the patients with suppressed bone turnover showed no osteoid lining of the trabeculae, no osteoblasts and no single or double tetracycline labels. Furthermore, the authors found that there were no significant differences in age, body mass index (BMI), bone mineral density (BMD), calcium and vitamin D intake, serum calcium, parathyroid hormone and 25hydroxyvitamin D between patients with normal and suppressed bone turnover. We think that, in the view of the aforementioned study, the correlation between duration of biphosphonate application and union time of hip fractures is an area that needs to be further explored.

This review has limitations because relatively few studies have been published looking at the effects of biphosphonates on hip fracture healing. As the majority of the patients were women, some or all of the conclusions of this study may not apply to men. The use of different operative techniques and implants between studies, as well as the presence of co-morbidities in some of the patients and the use of other drugs to treat them, perhaps influenced in some way our findings.

In conclusion, in the review of the published literature, it was found that the application of biphosphonates prior to a hip fracture, can have negative effects on its healing process, but this is not happening if they are applied after the fracture event. It was also found that there is no correlation between duration of biphosphonate treatment and union time of hip fractures. There is a need of additional studies to investigate the effects of biphosphonates on hip fracture healing. These studies need to be focused on healing time, non-union rates and the duration of treatment.

References

1. Kannus P, Parkkari J, Sievänen H, Heinonen A, Vuori I, Järvinen M. Epidemiology of hip fractures. Bone 1996;18:57-63.
2. Shivji FS, Green VL, Forward DP. Anatomy, classification and treatment of intracapsular hip fractures. Br J Hosp Med (Lond) 2015;76:290-5.
3. Sheehan SE, Shyu JY, Weaver MJ, Sodickson AD, Khurana B. Proximal Femoral Fractures: What the Orthopedic Surgeon Wants to Know-Erratum. Radiographics 2015;35:1624.
4. Mavrogenis AF, Panagopoulos GN, Megaloikonomos PD, Igoumenou VG, Galanopoulos I, Vottis CT, Karabinas P, Koulouvaris P, Kontogeorgakos VA, Vlamis J, Papagelopoulos PJ. Complications after Hip Nailing for Fractures. Orthopedics 2016;39:108-16.
5. Eriksen EF, Díez-Pérez A, Boonen S. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: a systematic review. Bone 2014;58:126-35.
6. Serrano AJ, Begoña L, Anitua E, Cobos R, Orive G. Systematic review and meta-analysis of the efficacy and safety of alendronate and zoledronate for the treatment of postmenopausal osteoporosis. Gynecol Endocrinol 2013;29:1005-14.
7. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY; European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Scientific Advisory Board of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF). Osteoporos Int 2013;24:23-57.
8. Russell RG, Mühlbauer RC, Bisaz S, Williams DA, Fleisch H. The influence of pyrophosphate, condensed phosphates, phosphonates and other phosphate compounds on the dissolution of hydroxyapatite in vitro and on bone resorption induced by parathyroid hormone in tissue culture and in thyroparathyroidectomised rats. Calcif Tissue Res 1970;6:183-96.
9. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, Compston JE, Drake MT, Edwards BJ, Favus MJ, Greenspan SL, McKinney R Jr, Pignolo RJ, Sellmeyer DE. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. J Bone Miner Res 2016;31:16-35.
10. Abrahamsen B. Adverse effects of bisphosphonates. Calcif Tissue Int 2010;86:421-35.
11. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, Cosman F, Lakatos P, Leung PC, Man Z, Mautalen C, Mesenbrink P, Hu H, Caminis J, Tong K, Rosario-Jansen T, Krasnow J, Hue TF, Sellmeyer D, Eriksen EF, Cummings SR; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356:1809-22.
12. Heckbert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med 2008;168:826-31.
13. Cummings SR, Schwartz AV, Black DM. Alendronate and atrial fibrillation. N Engl J Med 2007;356:1895-6.
14. Woo SB, Hellstein JW, Kalmar JR. Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws. Ann Intern Med 2006;144:753-61.
15. Shane E. Evolving data about subtrochanteric fractures and bisphosphonates. N Engl J Med 2010;362:1825-7.
16. Corrales LA, Morshed S, Bhandari M, Miclau T 3rd.Variability in the assessment of fracture-healing in orthopaedic trauma studies. J Bone Joint Surg Am 2008;90:1862-8.
17. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Hip

fracture incidence among the old and very old: a population-based study of 745,435 cases. Am J Public Health 1990;80:871-73.
18. Boonen S, Autier P, Barette M, Vanderschueren D, Lips P, Haentjens P. Functional outcome and quality of life following hip fracture in elderly women: a one-year prospective controlled study. Osteoporos Int 2004;15:87-94.
19. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. J Gerontol A Biol Sci Med Sci 2000;55:498-507.
20. Adachi JD, Ioannidis G, Berger C, et al. The influence of osteoporotic fractures on health related quality of life in community-dwelling men and women across Canada.Osteoporos Int 2001;12:903-8.
21. Hannan EL, Magaziner J, Wang JJ, et al. Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes. JAMA 2001;285:2736-42.
22. Ray NF, Chan JK, Thamer M, Melton LJ III. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24-35.
23. Cooper C, Campion G, Melton LJ III. Hip fractures in the elderly: a worldwide projection.Osteoporos Int 1992;2:285-9.
24. Davidson CW, Merrilees MJ, Wilkinson TJ, McKie JS, Gilchrist NL. Hip fracture mortality and morbidity - can we do better? N Z Med J 2001;114:329-32.
25. Magaziner J, Lydick E, Hawkes W, et al. Excess mortality attributable to hip fracture in white women aged 70 years and older. Am J Public Health 1997;87:1630-6.
26. Colon-Emeric C, Kuchibhatla M, Pieper C, et al. The contribution of hip fracture to risk of subsequent fracture: data from two longitudinal studies. Osteoporos Int 2003;14:879-83.
27. Cumming RG, Nevitt MC, Cummings SR. Epidemiology of hip fractures.Epidemiol Rev 1997;19:244-57.
28. Rubenstein LZ. Falls in older people: epidemiology, risk factors and strategies for prevention. Age Ageing 2006;35:37-41.
29. Gardner MJ, Brophy RH, Demetrakopoulos D, et al. Interventions to improve osteoporosis treatment following hip fracture: a prospective, randomized trial. J Bone Joint Surg Am 2005;87:3-7.
30. Solomon DH, Finkelstein JS, Katz JH, Mogun H, Avorn J. Underuse of osteoporosis medications in elderly patients with fractures. Am J Med 2003;115:398-400.
31. Colon-Emeric C, Lyles KW, House P, et al. Randomized trial to improve fracture prevention in nursing home residents. Am J Med 2007;120:886-92.
32. Plotkin LI, Weinstein RS, Parfitt AM, Roberson PK, Manolagas SC, Bellido T. Prevention of osteocyte and osteoblast apoptosis by bisphosphonates and calcitonin. J Clin Invest 1999;104:1363-74.
33. Weinstein RS, Roberson PK, Manolagas SC. Giant osteoclast formation and long-term oral bisphosphonate therapy. N Engl J Med 2009;360:53-62.
34. Einhorn TA. The cell and molecular biology of fracture healing. Clin Orthop Relat Res 1998;355:7-21.
35. Murakami H, Takahashi N, Sasaki T, Udagawa N, Tanaka S, Nakamura I, Zhang D, Barbier A, Suda T. A possible mechanism of the specific action of bisphosphonates on osteoclasts: tiludronate preferentially affects polarized osteoclasts having ruffled borders. Bone 1995; 17:137-44.
36. Sato M, Grasser W. Effects of bisphosphonates on isolated rat osteoclasts as examined by reflected light microscopy. J Bone Miner Res 1990;5:31-40.
37. Lenehan TM, Balligand M, Nunamaker DM, Wood FE Jr. Effect of EHDP on fracture healing in dogs. J Orthop Res. 1985;3:499-507.
38. Li J, Mori S, Kaji Y, Mashiba T, Kawanishi J, Norimatsu H. Effect of bisphosphonate (incadronate) on fracture healing of long bones in rats. J Bone Miner Res 1999;14:969-79.
39. Peter CP, Cook WO, Nunamaker DM, Provost MT, Seedor JG, Rodan GA. Effect of alendronate on fracture healing and bone remodeling in dogs. J Orthop Res 1996;14:74-9.
40. Adolphson P, Abbaszadegan H, Bodén H, Salemyr M, Henriques T. Clodronate increases mineralization of callus after Colles' fracture: a randomized, double-blind, placebo-controlled, prospective trial in 32 patients. Acta Orthop Scand 2000;71:195-200.
41. Rozental TD, Vazquez MA, Chacko AT, Ayogu N, Bouxsein ML. Comparison of radiographic fracture healing in the distal radius for patients on and off bisphosphonate therapy. J Hand Surg Am 2009;34:595-602.
42. Eriksen EF, Lyles KW, Colón-Emeric CS, Pieper CF, Magaziner JS, Adachi JD, Hyldstrup L, Recknor C, Nordsletten L, Lavecchia C, Hu H, Boonen S, Mesenbrink P. Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. J Bone Miner Res 2009;24:1308-13.
43. Prasarn ML, Ahn J, Helfet DL, Lane JM, Lorich DG. Bisphosphonate-associated femur fractures have high complication rates with operative fixation. Clin Orthop Relat Res 2012;470:2295-301.
44. Egol KA, Park JH, Rosenberg ZS, Peck V, Tejwani NC. Healing delayed but generally reliable after bisphosphonate-associated complete femur fractures treated with IM nails. Clin Orthop Relat Res 2014;472:2728-34.
45. Das De S, Setiobudi T, Shen L, Das De S. A rational approach to management of alendronate-related subtrochanteric fractures. J Bone Joint Surg Br 2010;92:679-86.
46. Teo BJ, Koh JS, Goh SK, Png MA, Chua DT, Howe TS. Post-operative outcomes of atypical femoral subtrochanteric fracture in patients on bisphosphonate therapy. Bone Joint J 2014;96:658-64.
47. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005;90:1294-301.
48. Li C, Mori S, Li J, Kaji Y, Akiyama T, Kawanishi J, Norimatsu H. Long-term effect of incadronate disodium (YM-175) on fracture healing of femoral shaft in growing rats. J Bone Miner Res 2001;16:429-36.
49. Manabe T, Mori S, Mashiba T, Kaji Y, Iwata K, Komatsubara S, Yamamoto T. Effect of dosing interval duration of intermittent ibandronate treatment on the healing process of femoral osteotomy in a rat fracture model. Calcif Tissue Int 2012;90:193-201.
50. Lin TL, Wang SJ, Fong YC, Hsu CJ, Hsu HC, Tsai CH. Discontinuation of alendronate and administration of bone-forming agents after surgical nailing may promote union of atypical femoral fractures in patients on long-term alendronate therapy. BMC Res Notes 2013;6:11.
51. Kim TY, Ha YC, Kang BJ, Lee YK, Koo KH. Does early administration of bisphosphonate affect fracture healing in patients with intertrochanteric fractures? J Bone Joint Surg Br 2012;94:956-60.
52. Lyles KW, Colón-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, Hyldstrup L, Recknor C, Nordsletten L, Moore KA, Lavecchia C, Zhang J, Mesenbrink P, Hodgson PK, Abrams K, Orloff JJ, Horowitz Z, Eriksen EF, Boonen S; for the HORIZON Recurrent Fracture Trial. Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture. N Engl J Med 2007;357:nihpa40967.
53. Harding AK, W-Dahl A, Geijer M, Toksvig-Larsen S, Tägil M. A single bisphosphonate infusion does not accelerate fracture healing in high tibial osteotomies. Acta Orthop 2011;82:465-70.
54. Gong HS, Song CH, Lee YH, Rhee SH, Lee HJ, Baek GH. Early initiation of bisphosphonate does not affect healing and outcomes of volar plate fixation of osteoporotic distal radial fractures. J Bone Joint Surg Am 2012;94:1729-36.
55. Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S, Novack D. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tissue Int 2009;85:37-44.