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Review Article

Can Bisphosphonates Prevent Recurrent Fragility Fractures? A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Sang Yoon Lee MD, PhD [a,b], Se Hee Jung MD, PhD [a], Shi-Uk Lee MD, PhD [a,c], Yong-Chan Ha MD, PhD [d], Jae-Young Lim MD, PhD [c,e,*]

[a] Department of Rehabilitation Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea
[b] Seoul National University Institute on Aging, Seoul, Republic of Korea
[c] Department of Rehabilitation Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[d] Department of Orthopedic Surgery, Chung-Ang University College of Medicine, Seoul, Republic of Korea
[e] Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, Seongnam-si, Gyeonggi-do, Republic of Korea

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A B S T R A C T

Objectives: Although a few trials have explored whether bisphosphonates (BPs) prevented recurrent fragility fractures (FFs), little is known about the secondary preventative effects of BPs. Thus, we performed a meta-analysis to examine the effects of BPs on prevention of subsequent fractures, mortality, and on bone metabolic and functional parameters related to FF. We compared BP and control groups.
Design: A meta-analysis of randomized controlled trials was conducted.
Setting and Participants: Twelve randomized controlled trials that included 5670 participants investigating the effects of BPs following FF were retrieved from PubMed, Embase, and the Cochrane Library.
Measures: We performed a pairwise meta-analysis using fixed- and random-effects models.
Results: BPs exhibited significant secondary preventative effects after FF compared with controls [overall standardized mean difference = 0.766; 95% confidence interval (CI) 0.493–1.038; $P < .001$]. The risks of subsequent fracture (odds ratio = 0.499; 95% CI 0.418–0.596; $P < .001$) and mortality (odds ratio = 0.662; 95% CI 0.511–0.858; $P = .002$) decreased in the BP groups. Bone mineral density, bone turnover marker levels, pain at the fracture site, and health-related quality of life also differed significantly between the groups.
Conclusions/Implications: Our meta-analysis revealed that BPs administered after FF potentially prevented subsequent fractures and reduced mortality. Positive effects in terms of pain, quality of life, and increased bone mineral density and bone metabolism were also verified regardless of the fracture sites and the administration types (oral or intravenous). Therefore, more active BPs use is recommended to prevent recurrent fragility fractures.
Level of Evidence: Level I, meta-analysis.

A fragility fracture (FF) is a fracture that occurs after minimal trauma, such as a fall from a standing height or less, or without any identifiable trauma.[1,2] Typical FFs in patients with osteoporosis include those of the proximal femur (hip), vertebral body (spine), and distal forearm (wrist).[3] As hip and vertebral fractures are associated with particularly high levels of morbidity and mortality,[4] FFs consume extensive healthcare resources associated with high medical costs.[5] Furthermore, an FF per se is an important risk factor for recurrent fracture.[6] One meta-analysis found that patients with a history of fracture were at 1.83–2.03 times increased risk of subsequent fractures.[7] Therefore, it is essential to prevent re-fracture.

Of the several therapeutic options, pharmacotherapy for osteoporosis with bisphosphonates (BPs) is one of the most popular and well-investigated treatments. One large cohort study including 31,069 participants with FFs found that anti-osteoporotic therapy was associated with a 40% decrease in the 3-year risk of subsequent

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* Address correspondence to Jae-Young Lim, MD, PhD, Department of Rehabilitation Medicine, Seoul National University Bundang Hospital, 82 Gumi-ro 173 Beon-gil, Bundang-gu, Seongnam-si, Gyeonggi-do 13620, Republic of Korea.
E-mail address: drlim1@snu.ac.kr (J.-Y. Lim).

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fracture.[8] Interestingly, 1 nationwide study showed that re-fracture risk was associated with BP therapy compliance.[9]

Only a few randomized controlled trials (RCTs) have explored whether BPs prevented recurrent FF, and little is known about the secondary preventative effects. In this meta-analysis, we explored whether BPs (compared with placebos) prevented subsequent fracture and reduced mortality (primary outcomes) and whether they improved metabolic and functional parameters associated with FFs (secondary outcomes). We hypothesized that subjects taking BPs after FFs would fare better.

Methods

Search Methods for Identifying Studies

The meta-analysis was conducted in line with the updated Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) guidelines.[10] PubMed-Medline, Embase, and Cochrane Library searches were performed in September 2017 using the following key terms: (Spinal Fractures OR Vertebral Fracture OR Compression Fracture OR Hip Fractures OR Femoral Neck Fractures OR Femur Intertrochanteric Fracture OR Colles Fracture OR Radius Fracture OR Fragility Fracture OR Osteoporotic Fractures) AND (Bisphosphonates OR Diphosphonates OR Alendronate OR Clodronic Acid OR Etidronic Acid OR Risedronate OR Pamidronate OR Ibandronate OR Zoledronic Acid OR Antiresorptive Agents) AND (Refracture OR Subsequent Fracture OR Second Fracture OR Second Contralateral Fracture OR Recurrent Fracture OR Mortality OR Bone Mineral Density OR Bone Turnover OR Bone Metabolism OR Bone Remodeling OR Bone Regeneration OR Bone Resorption). An overview of the search strategy is presented in Supplementary Appendix A. We included all RCTs comparing BPs and placebos after FFs. We imposed no language restriction.

Study Selection Criteria

The identified records were saved to EndNote software (X7.2; Thomson Reuters). Two independent reviewers (SYL, JYL) first screened all titles and abstracts to identify relevant investigations. Inclusion criteria were (1) articles reporting an RCT that (2) described the effects of BPs after FFs. All types of BPs (alendronate, clodronate, etidronate, risedronate, pamidronate, ibandronate, and zoledronate) were included. All controls received placebos. Concomitant therapies (such as calcium carbonate or vitamin D) were permitted if both the BP and control groups received the therapies. Reviews, basic science articles, comments, letters, and protocols were excluded. When updates of earlier studies were identified, we used only the latest updates.

Outcome Measures and Data Extraction

The primary outcomes of interest were subsequent fracture and mortality after FFs. All new fractures were diagnosed clinically and radiographically. The secondary outcomes were (1) bone mineral density (BMD) measured by dual energy X-ray absorptiometry at and around the fracture site; (2) the levels of bone turnover markers (serum levels of ionized calcium, parathyroid hormone, and N-telopeptide); (3) pain at the fracture site measured using a visual analog or a numerical rating scale; and (4) health-related quality of life. We performed subgroup analyses based on types of BP (oral vs intravenous) and fracture sites (hip vs spine vs wrist). For every eligible study, the following data were extracted and entered into a spreadsheet by the 2 reviewers (SYL, JYL): first author's family name, year of publication, number of patients, mean age at the time of FF, enrolment time, BP type used, treatment duration, follow-up duration, and outcomes.

Quality Assessment and Publication Bias

Two authors (SYL, JYL) independently evaluated study quality using the criteria of the Cochrane Handbook for Systematic Reviews of Interventions.[11] These included (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome data; (5) any incomplete outcome data addressed; (6) selective reporting; and (7) other bias. We assessed publication bias using the Begg funnel plot[12] and the Egger test.[13]

Statistical Analysis

Effect sizes were computed as odds ratios (ORs) for primary outcomes (subsequent fracture and mortality) and standardized mean differences (SMDs)[14] for secondary outcomes (the magnitude of the pretest–posttest difference for each outcome). To derive overall Hedges g-pooled effect sizes, ORs were converted to SMDs. Pooled SMDs were computed separately for the control and treatment groups of each study. Heterogeneity among comparable studies was explored using the χ^2 and I^2 tests. Values of $P > .1$ and $I^2 < 50\%$ were considered statistically significant. As significant heterogeneity was evident among the selected studies ($P < .001$ and $I^2 = 87.5\%$), we used a random-effects model to quantify the pooled effect size of the included studies. BMD ($P < .001$ and $I^2 = 83.4\%$) and bone turnover marker levels ($P = .024$ and $I^2 = 80.3\%$) were also analyzed using a random-effects model. However, we employed a fixed-effects model to analyze the effects on subsequent fracture ($P = .337$ and $I^2 = 11.3\%$), mortality ($P = .252$ and $I^2 = 23.7\%$), pain at the fracture site ($P = .570$ and $I^2 = 0.0\%$), and health-related quality of life ($P = 1.000$ and $I^2 = 0.0\%$). In addition, we performed subgroup analyses by the type of BP (oral and intravenous) and fracture site (hip, wrist, and spine). The Q-test for heterogeneity was used when performing subgroup analyses.[15] All analyses were conducted with the aid of Comprehensive Meta-Analysis software (v 3.3; Biostat, Englewood, NJ). The study did not require institutional review board approval because we did not personally enroll any human participants.

Results

Description of Included Studies

The primary database search yielded 360 records. After duplicates were removed, the titles and abstracts of 149 articles were initially screened, and 24 selected for full-text review. The full texts were read, and 12 met all quality-assessment inclusion criteria.[16–27] The studies selected for final inclusion (or exclusion) are shown in Figure 1, and the characteristics of the included studies are summarized in Table 1. In terms of quantitative analysis, these 12 RCTs (published from 1996 to 2016) fulfilled our inclusion criteria. The studies identified for meta-analysis included 5670 participants. Study sample sizes varied from 32 to 2127 (16–1065 cases and 16–1062 controls). The selected studies included 2857 patients prescribed BPs and 2813 given placebos. Follow-up duration ranged from 1 month to 3 years.

Results after Analysis

BPs significantly prevented secondary FFs [overall Hedges g-pooled SMD = 0.766; 95% confidence interval (CI) 0.493–1.038; $P < .001$] (Figure 2). The risks of subsequent fracture (OR = 0.499; 95% CI 0.418–0.596; $P < .001$) and mortality (OR = .662; 95% CI 0.511–0.858; $P = .002$) after FF were reduced in the BP group. In terms of secondary outcomes, BMD (pooled SMD = 0.809; 95% CI 0.261–1.357; $P = .004$), bone turnover marker levels (pooled SMD = 1.805; 95% CI 0.844–2.766; $P < .001$), pain at the fracture site (pooled SMD = 0.629; 95% CI 0.210–1.048; $P = .004$), and health-