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Efficacy and safety of bisphosphonates in management of low bone density in inflammatory bowel disease

A meta-analysis

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Abstract

This study aims to determine whether bisphosphonates are safe, as well as effective against bone mineral loss in inflammatory bowel disease (IBD). A computerized search of electronic databases from 1966 to 2016 was performed. Randomized controlled trials (RCTs) were included in this review to evaluate the role of bisphosphonates in the management of osteoporosis in IBD patients. A revised 7-point Jadad scale was used to evaluate the quality of each study. Overall, 13 RCTs and 923 patients met the inclusion criteria of this meta-analysis. The result showed that bisphosphonates decreased bone mass density (BMD) loss at the lumbar spine ($P = 0.0002$), reduced the risk of new fractures ($P = 0.01$), and retained the similar adverse events ($P = 0.86$). Bisphosphonates may provide protection and safety against bone mineral loss in IBD patients.

Abbreviations: BMD = bone mass density, CI = confidence intervals, IBD = inflammatory bowel disease, MD = mean difference, RCTs = randomized controlled trials.

Keywords: bisphosphonates, bone density, inflammatory bowel disease, meta-analysis

1. Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting alterative inflammatory disease that mostly occurs in the ileum and the perianal region.[1] Increasing prevalence of bone mineral loss has been observed in patients with IBD, confusing both physicians and afflicted patients for a long time. Approximately 18% to 42% of the IBD patients have been reported to have prevalence of osteoporosis, whereas 40% to 50% of the IBD patients have been observed to have frank osteopenia.[2,3] Compared with normal subjects, it results in significant morbidity due to the increased risk of fracture.[4] Indeed, vertebral fractures have been reported to be notably high at 22% in IBD patients.[5]

The key etiology of low bone density in IBD patients is the high dose of glucocorticoids. Patients suffer from a high risk of fracture when undergoing therapies recommended by the actual guidelines for IBD.[6] Furthermore, there are some adverse effects of steroids used in these therapies, such as reduction in the intestinal calcium absorption, increased renal calcium excretion, and inhibited osteoblast activity.[7,8] Another significant risk is high systemic inflammatory activity, which includes the tumor necrosis factor, interleukin-1-β, and osteoprotegerin.[9] These cytokines may stimulate osteoblasts synthesis and the secretion of receptor-activated nuclear factor kappa B ligand, thereby promoting proliferation and differentiation of osteoclasts.[10] Other factors, such as genetic influence, malnutrition, disturbance of calcium homeostasis, low body mass index, malabsorption, hypogonadism,[11,12] and other lifestyle factors, such as smoking[13] or being sedentary, may contribute to the reduction of the bone mass.

In general medical practice, patients with significantly low *T*-scores are often managed with bisphosphonates to prevent the overall osteoporotic process. Bisphosphonates have been proven as potent antiresorptive agents in postmenopausal osteoporosis and have been known to cause a significant increase in the bone density of the general population.[14–17] This treatment generally depletes the level of systemic circulation of estrogen and androgen involved in the maintenance of bone mass through the suppression of osteoclast-mediated bone reabsorption and the promotion of bone formation.[18,19] Bisphosphonates are designated as the current standard treatment for glucocorticoid-induced osteoporosis,[20] such as zoledronate, alendronate, risedronate, ibandronate, pamidronate, clodronate, and etidronate. In addition, bisphosphonates also have a broad application in the treatment of steroid-induced osteoporosis in IBD patients. Some randomized controlled trials (RCTs) have been conducted with oral or intravenous bisphosphonate to IBD patients with low bone mass. However, no general agreement regarding the suggestions of these studies has been presented.

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The relationship between the use of different bisphosphonates and the bone mineral is crucial for guiding IBD patients with osteoporosis. Thus, the aim of this review is to evaluate the efficacy and safety of bisphosphonates in the management of low bone density in IBD patients.

2. Materials and methods

2.1. Search strategy

A computerized search was performed on the electronic databases such as PubMed Medline (from 1966 to March 2016), EMBASE (from 1980 to March 2016), Cochrane library (updated to March 2016) using the following keywords: Crohn disease, IBD, ulcerative colitis, bisphosphonates, etidronate, alendronate, risedronate, ibandronate, and zoledronate. Relevant published studies, including those reported in any language, were included for this review. Full articles containing abstracts that indicated the use of RCT, particularly in the evaluation of the role of bisphosphonates in the management of osteoporosis in IBD patients, were retrieved to obtain more information. The data sources were complemented by manually searching the references cited in the retrieved full articles. Ethical approval of this study was not necessary, because this article did not involve patients.

2.2. Study selection

The studies were selected using the following criteria: use of RCT design, population of interest: IBD patients with osteopenia or osteoporosis, intervention: insistent bisphosphonates treatment versus placebo, and assessment of outcome: change in bone mass density (BMD) at lumbar, change in BMD at the hip, the incidence of fracture, and adverse events. Meanwhile, the exclusion criteria are the following: letters, case reports, guidelines, meeting proceeding, case–control study, and studies with duplicated data and experimental trials on animal.

2.3. Assessment of study quality

Two reviewers assessed the methodological quality of each study independently. Studies that satisfied the inclusion criteria were evaluated using the revised 7-point Jadad scale.[21] The scale consists of 4 aspects: generation of allocation sequence (2 points), allocation concealment (2 points), investigator blindness (2 points), and withdrawals and dropouts (1 point). Total scores <4 mean low quality and ≥ 4 mean high quality.

2.4. Data extraction

Two reviewers independently extracted data from eligible studies using the previously mentioned inclusion criteria (study design, participants, interventions, and outcome). The extracted data included the following: the first author, trial design, population, sex ratio, age, duration of follow-up, change in BMD at lumbar, change in BMD at hip, the incidence of fracture, and adverse events. If some necessary original data cannot be acquired from publications, the author of the source was contacted to obtain detailed information. Agreements on the data between the 2 reviewers were stipulated. Another reviewer and expert (HM) was consulted for the evaluation of discrepancies that persisted in the data.

2.5. Data analysis

Data analysis was performed using the RevMan5.1 software (Cochrane Collaboration, Copenhagen, Denmark: The Nordic Cochrane Centre). For dichotomous variables, we adopted the risk ratio and the 95% confidence intervals (CI) as summary statistics. For continuous variables, we calculated the mean difference (MD) and the 95% CI. Both significances were set at $P < 0.05$. We used chi-square and I^2 tests to assess heterogeneity among the trials, in which $P < 0.10$ means a significant value. A fixed-effect model was selected to pool the results when there was no significant statistical heterogeneity. Otherwise, the random-effect model was adopted.

3. Results

3.1. Study identification and selection

The initial computerized search generated 434 potentially relevant papers. After reading the titles, the abstracts and the full articles, 13 RCTs[22–34] were determined to have met the inclusion criteria of the systematic review. The whole process of the search is shown in Fig. 1. In total, 923 patients (bisphosphonates 482 and control 441) were variable in the management of IBD patients with low bone destiny problem.

3.2. Study characteristics

Table 1 presents a summary of the included studies in this meta-analysis. The studies included were published during the years from 2000 to 2014. A total of 8 studies were conducted in Europe, 1 from Denmark, 2 from the United Kingdom, 2 from Germany, 1 from Italy, 1 from France, 1 from the Netherlands, and the other 3 studies were separately conducted in Canada, Australia, and Japan. Meanwhile, 8 trails reported Crohn disease, 1 article reported ulcerative colitis, and the others were about IBD. The date of follow-up ranged from 8 weeks to 42 months.

All the 13 included studies were designed as RCT. In Figs. 2 and 3, the risk of bias tool in RevMan5.1 software was used to evaluate the risk of bias in these articles.

3.3. Change% in BMD at lumbar spine

In Fig. 4, 7 studies[22,24,26–28,30,33] with a total number of 526 patients (57%) recorded change% (change in bone destiny from the baseline) at lumbar spine. Around 266 patients (55%) were treated with bisphosphonates and 199 patients (45%) used placebo. Using a random effect model, we observed a statistical difference in terms of change % in BMD at lumbar spine (MD = 1.72, 95% CI: 0.8, 2.63, $P = 0.0002$) in favor of the control ($I^2 = 96\%$ was for heterogeneity).

3.4. Change% in BMD at hip

In Fig. 5, 7 studies[22,23,26–28,30,33] with a total number of 496 patients (54%) reported change% at their hips. There were 266 patients (55%) with bisphosphonates and 230 patients (52%) with placebos. Using a random effect model, there was no apparent statistical difference in terms of change% at the hips (MD = 0.46, 95% CI: −0.02, 0.94, $P = 0.06$) in favor of the control ($I^2 = 83\%$ was for heterogeneity).

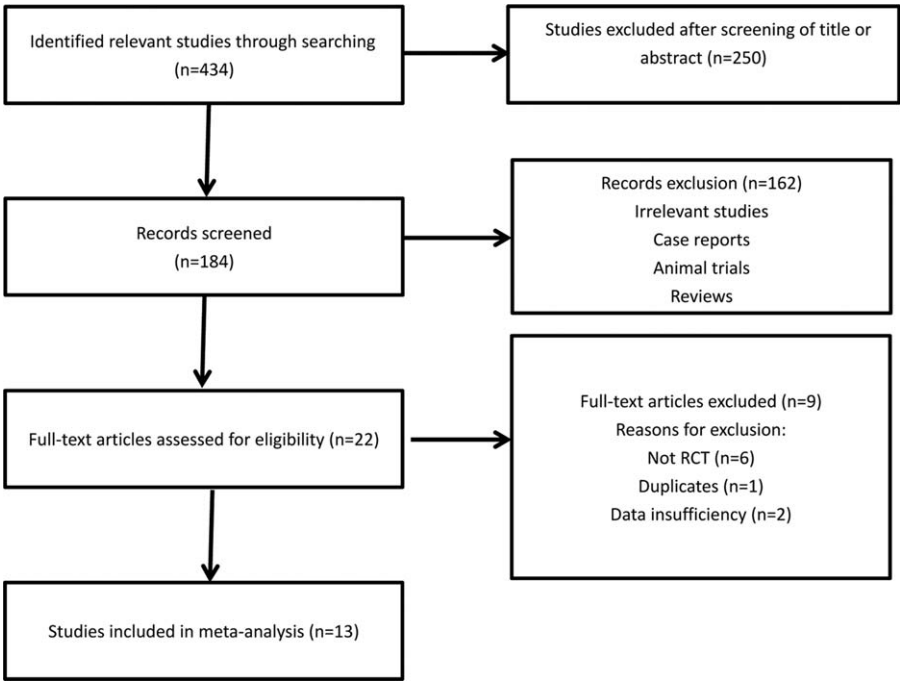

Figure 1. The whole process of search.

Table 1

The summary of this meta-analysis.

First author	Diagnosis	Country	Date of publication	Type of trial	No. of patients		Mean age		Gender (male/female)	
					bio	con	bio	con	bio	con
Haderslev	CD	Denmark	2000	RCT	17	15	44	44	–	–
Bartram	CD	UK	2003	RCT	37	37	45.1	43.5	12/22	20/14
Von Tirpitz	CD	Germany	2003	RCT	35	13	35.7	37.2	17/18	9/4
Palomba	IBD	Italy	2005	RCT	40	41	52.3	51.4	–	–
Siffledeen	CD	Canada	2005	RCT	72	71	40	40.1	34/38	37/34
Henderson	IBD	Australia	2006	RCT	23	25	49.9	47.2	10/13	13/12
Abitbol	IBD	France	2007	RCT	33	34	30	30	–	–
Kitazaki	UC	Japan	2009	RCT	16	18	41.2	38.1	4/2	5/4
Kriel	IBD	UK	2010	RCT	39	39	42.6	42.5	–	–
Sbrocchi	CD	Canada	2010	RCT	7	6	14.6	14.6	13/26	20/19
Klaus	CD	Germany	2011	RCT	54	32	36.8	33.8	11/9	10/10
Soo	CD	Canada	2012	RCT	45	43	39.8	36.7	16/17	17/16
Van bodegraven	CD	Netherlands	2014	RCT	64	67	43	42	23/22	21/22

Mean BMI, kg/m^2		Postmenopausal		Follow-up	Intervention		
bio	con	bio	con		bio	con	CM
23±3	22±2	3	4	12 mo	Alendronate 10 mg daily p.o.	Placebo	Ca 1 g + vitamin D 400 IU
22.6±3.0	23.5±3.9	9	8	12 mo	Pamidronate 30 mg 3 monthly i.v.	Ca 500 mg vitamin D 400 IU	Ca 500 mg vitamin D 400 IU
22.4±0.8	25.11±1.9	–	–	27 mo	Ibandronate every 3 mo i.v.	Ca 800 mg vitamin D 1000 IU	Ca 800 mg vitamin D 1000 IU
24.4±1.9	25.2±2.1	40	41	12 mo	Risedronate 35 mg weekly p.o.	Placebo	Ca 1500 mg
24.2±3.9	24.0±4.6			24 mo	Etidronate 400 mg for 14 d in every 3 mo p.o.	Ca 500 mg vitamin D 400 IU	Ca 500 mg vitamin D 400 IU
25.3±3.6	25.7±3.7	5	9	12 mo	Risedronate 5 mg daily p.o.	Placebo + Ca 600 mg	Ca 600 mg per day
21.7	21.4	0	0	12 mo	Clodronate 900 mg every 3 mo i.v.	Placebo + Ca 1 g vitamin D 800 IU	Ca 1 g + vitamin D 800 IU
19.1±2.5	19.3±2.6	–	–	12 mo	Alendronate 5 mg daily p.o.	Alfacalcidol 1 μg/d	
22.4±2.9	21.5±3.5	–	–	8 wk	Risedronate 35 m weekly	Placebo	Ca 500 mg vitamin D 440 IU
24	26	0	0	6 mo	Zoledranate 0.066 mg/kg i.v.	Placebo	–
22.8±2.22	21.9±2.87	1	0	42 mo	Ibandronate 1 mg every 3 mo i.v.	Ca 800 mg vitamin D 1000 IU	–
22.3±3.8	21.8±3.29	–	–	24 mo	Risedronate 35 mg/kg	Placebo + Ca 500 mg vitamin D 400 IU	Ca 500 mg vitamin D 400 IU
25.5±5.3	23.7±4.6	–	–	24 mo	Risedronate 35 mg/kg	Placebo + Ca 1 g vitamin D 800 IU	Ca 1000 mg vitamin D 800

bio = bisphosphonates group, BMI = body mass index, Ca = calcium, CD = Crohn disease, CM = concomitant medications, con = control group, i.v. = intravenous injection, IBD = inflammatory bowel disease, p.o. = per os, RCT = randomized controlled trial, UC = ulcerative colitis.

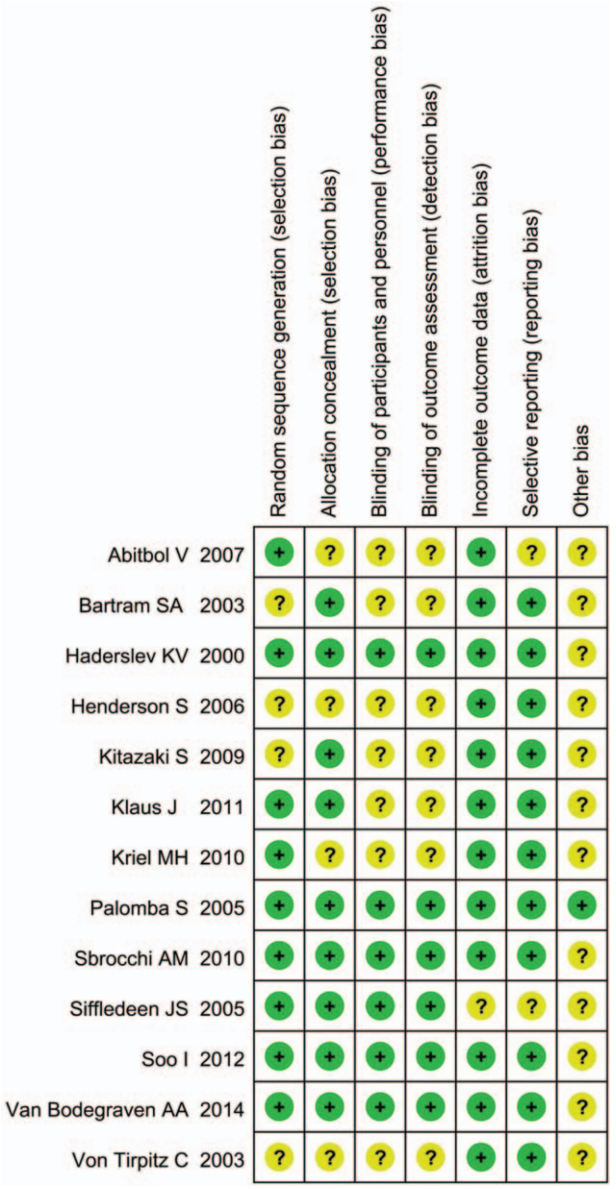

Figure 2. Risk of bias summary.

3.5. New fracture

In Fig. 6, 7 studies[22,25,27–29,32,34] with a total number of 480 patients (52%) recorded the incidence of new fracture. Particularly, 7 events (2.8%) that involve 247 patients with bisphosphonates were reported new fracture, whereas 20 events (8.6%) occurred in 232 patients with placebo. Using a fixed-effect model, we observed no apparent statistical difference in terms of new fracture (Odds ratio (OR) = 0.33, 95% CI: 0.14, 0.77, $P = 0.01$) in favor of the control ($I^2 = 0\%$ was for heterogeneity).

3.6. Adverse events

In Fig. 7, 9 studies[22,24–29,32,33] with a total number of 629 patients have reported adverse events. Particularly, 335 patients were treated with bisphosphonates and 294 patients were given placebos. Using a fixed-effect model, there was no obvious statistical difference in terms of adverse events (OR = 1.04, 95% CI: 0.65, 1.69, $P = 0.86$) in favor of the control ($I^2 = 30\%$ was for heterogeneity).

4. Discussion

Although osteoporosis in IBD patients is highly prevalent, low BMD has been clinically silent and patients have been universally asymptomatic. Osteoporosis increases the significant risk of severe fracture even after low-trauma fractures.[35] Thus, fracture prevention becomes a mandatory question. Bisphosphonates therapy has been suggested to be applied in IBD patients with low bone mineral mass. However, there has been little evidence on this issue. The primary aim of this article is to evaluate the efficiency of bisphosphonates in the management of IBD patients with low bone mass.

4.1. Summary of main results

This meta-analysis shows the positive relationship between the use of different bisphosphonates and the change in percent in BMD at the lumbar spine. Incidents of fracture are significantly high without bisphosphonates management. No significant different has been observed between the bisphosphonates group and control group in terms of change% in BMD in hip and adverse events.

We found that bisphosphonates are beneficial to increase lumbar BMD and reduce fracture incidents. This is inconsistent with Guo et al[36] study in which he claimed that bisphosphonates

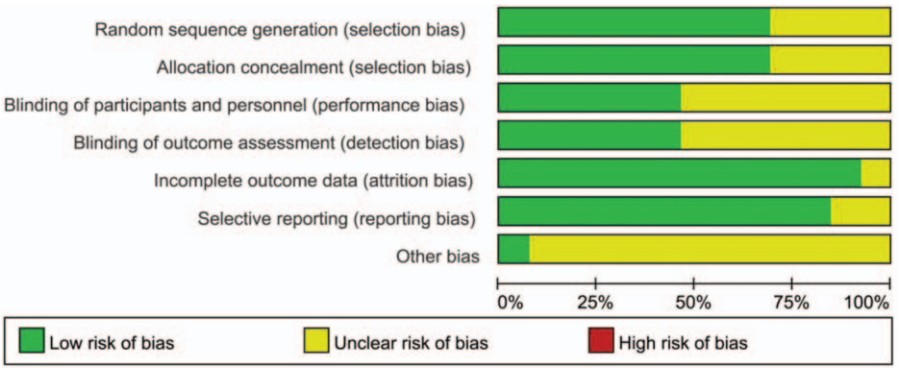

Figure 3. Risk of bias graph.

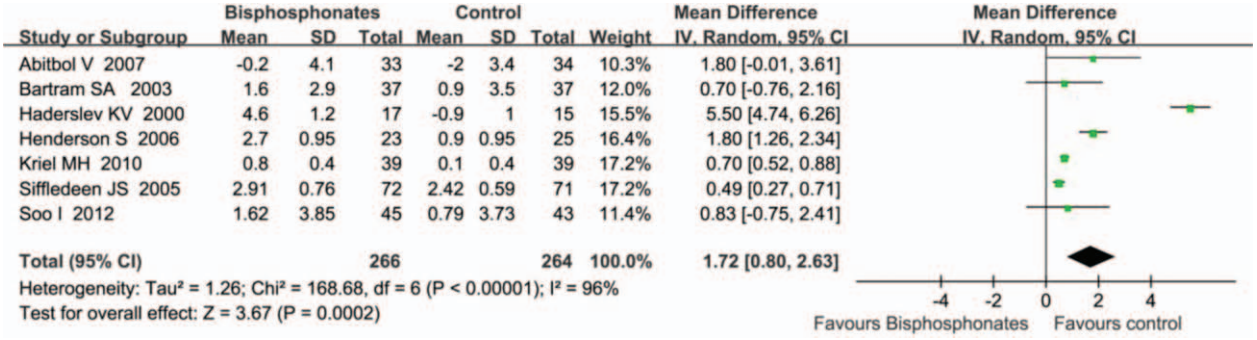

Figure 4. Forest plots of change% in bone mass density at lumbar spine.

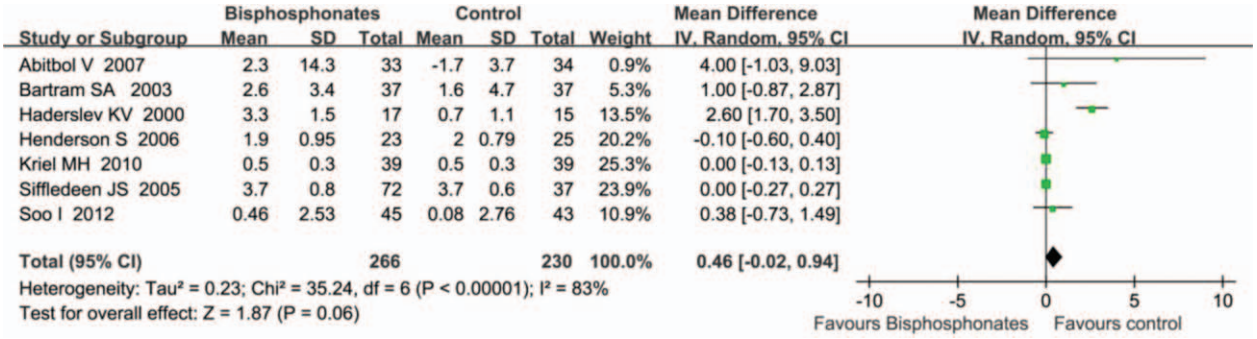

Figure 5. Forest plots of change% in bone mass density at hip.

could increase the BMD at the hips not at the spine. The reason for this may be that his study is limited to patients with Crohn disease. Previous studies[10,37] have suggested that Crohn disease is specifically associated with a significant negative effect on BMD, whereas ulcerative colitis does not affect BMD after osteoactive medicine. Melek and Sakuraba[38] reported that the amount bisphosphonates was greater than that of the controls in increasing BMD both at the lumbar spine and at the hip. In sensitive analysis, we found that there was a significant difference between bisphosphonates and control after excluding Henderson et al[27] study ($P=0.03$) in term of change% at the hips. In fact, Henderson found that the improvement in bone density with risedronate occurred at the entire hip and femoral neck in addition to the lumbar spine. Thus, bisphosphonates have been thought to be efficient in treating low bone mass in IBD patients.

As for its safety, bisphosphonates demonstrated tolerance with no difference in adverse events as compared with the placebo group. Adverse events include abdominal pain, diarrhea, nausea, vomiting, rash, and muscle pain, and most symptoms were mild and temporary. In fact, the application of some bisphosphonates may not influence the microenvironment of the disease, as observed from the evidence of routine biochemistry and inflammatory markers.[27]

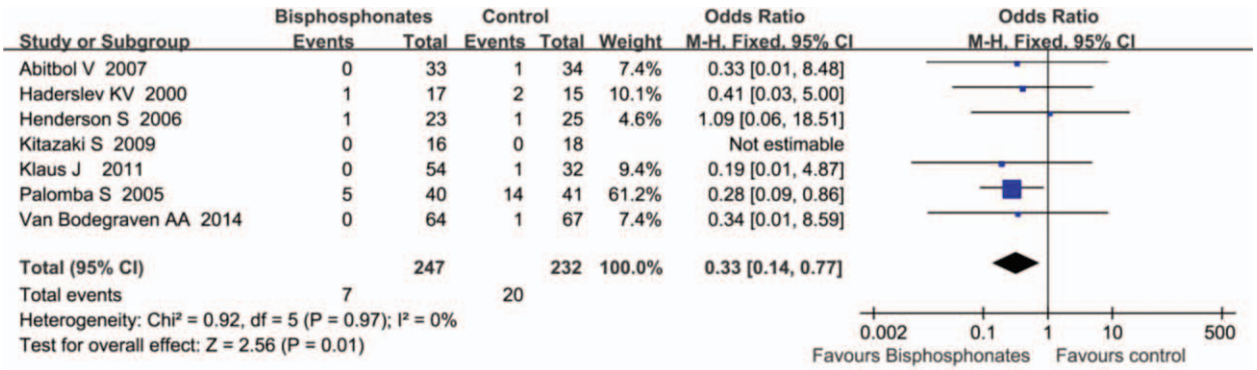

Figure 6. Forest plots of fracture.

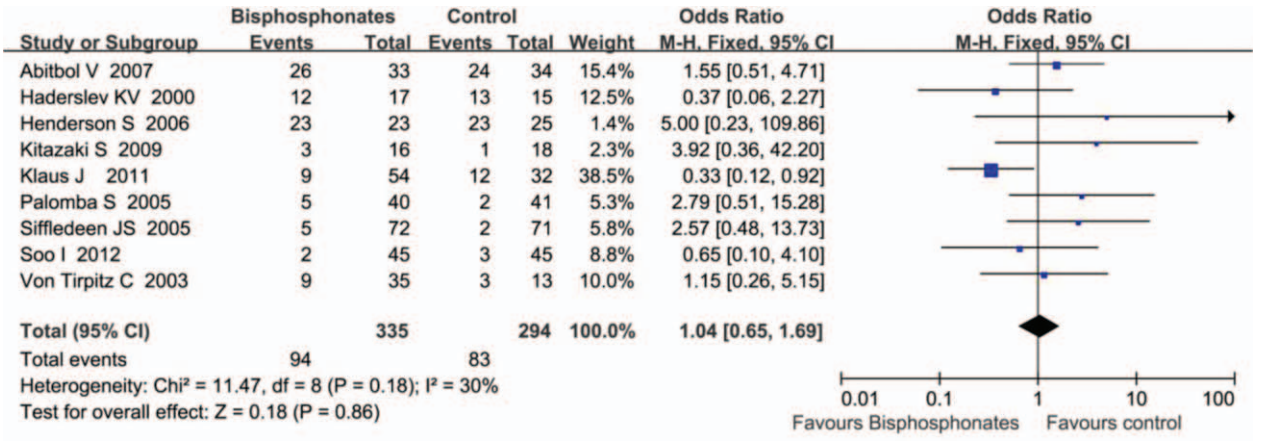

Figure 7. Forest plots of adverse events.

4.2. Strengths and weaknesses

This meta-analysis has the following strengths: the authors designed a comprehensive search strategy to minimize publication bias. Only RCT were considered in this article. The total sample size was large enough. The result of sensitive analysis is stable.

However, there are some limitations in this article: first, the geographical difference. Particularly, these authors mostly came from different districts. Furthermore, the diversity of different ethnic populations may have different perceptions about this disease. Second are age and sex. One study reported about adolescence patients, whereas 5 articles contained postmenopausal woman. Third, the category and dosages of bisphosphonates are different, which may minimize the available scope of this study.

5. Conclusion

Although IBD patients suffer from the high risk of low bone density, sustained deteriorative systemic bone loss may not be inevitable. Individualized treatment with bisphosphonates for IBD patients with osteoporosis can be an alternative in clinical therapy.

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