

# The role of neridronate in the management of osteoporosis: A meta-analysis

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## Abstract

**Background.** It is estimated that 1 in 3 women and 1 in 5 men over the age of 50 worldwide will experience an osteoporosis fracture during their lives. Neridronate is a third-generation bisphosphonate with established efficacy in metabolic bone disease. It can be used in the treatment of osteoporosis.

**Objectives.** We aimed to conduct a meta-analysis of the effect of neridronate on the treatment of osteoporosis.

**Materials and methods.** The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used to guide the present study. We searched PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) for reports published until August 31, 2021, related to neridronate and osteoporosis. The modification of the bone mineral density (BMD, g/cm<sup>2</sup>) of the patient is the core indicator for neridronate treatment.

**Results.** Significant increases in the BMD of the lumbar spine (mean difference (MD) = 5.99, 95% confidence interval (95% CI): 3.96–8.02), femoral neck (MD = 4.51, 95% CI: 2.01–7.01) and total hip (MD = 2.55, 95% CI: 2.10–3.00) were found. Greater improvement in the BMD of the lumbar spine and femoral neck could also be detected in patients with postmenopausal osteoporosis than with other causes of osteoporosis. Moreover, significant decreases in serum C-telopeptide of collagen type I (sCTX, standardized mean difference (SMD) = –0.84, 95% CI: –1.32––0.37) and bone alkaline phosphatase (ALP, MD = –5.29, 95% CI: –7.31––3.26) levels were observed.

**Conclusions.** The pool analysis of the selected clinical trials indicates the great benefit of neridronate in improving the condition of patients with osteoporosis of all causes, particularly patients with postmenopausal osteoporosis, which causes an increase in BMD as well as in sCTX and bone ALP levels.

**Key words:** osteoporosis, bone mineral density, neridronate, bisphosphonates, meta-analysis

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## Introduction

Osteoporosis is a condition distinguished by gradually decreasing bone mass and deteriorating bone structure.<sup>1</sup> It is a serious health problem, which is characterized by an increased susceptibility to fragility fractures, leading to poor quality of life and increased morbidity and mortality. It is estimated that 1 in 3 women and 1 in 5 men over the age of 50 worldwide will experience an osteoporotic fracture during their lives.<sup>2</sup> Osteoporosis puts heavy economic burden on patients and society.<sup>3</sup> Although 1/3 of patients with osteoporosis are postmenopausal women, many risk factors can lead to the disease.<sup>4</sup> Despite the cause of osteoporosis, various medications are available to prevent fractures.

Besides the supplementation of calcium and vitamin D, oral bisphosphonates are the most widely used agents in the treatment of osteoporosis.<sup>5,6</sup> A meta-analysis has shown that bisphosphonates are effective in treating thalassemia-induced osteoporosis.<sup>7</sup> However, the broad use of oral bisphosphonates, their low bioavailability,<sup>8</sup> and the fact that they occasionally cause severe gastrointestinal side effects<sup>9</sup> lead to low adherence and compliance by patients. These limitations resulted in the development of intermittent intravenous infusions of bisphosphonates, including neridronate. Neridronate is an amino-bisphosphonate with a structure similar to alendronate and pamidronate. It inhibits bone resorption without changing the mineralization process.<sup>10</sup> Neridronate has been evaluated in several clinical trials for the treatment of osteogenesis imperfecta<sup>11–17</sup> and Paget's disease<sup>18–21</sup> to prevent bone loss and increase bone mineral density (BMD). It can also be used in the treatment of osteoporosis.

## Objectives

In this paper, we screened and selected 6 randomized control trials (RCTs) evaluating the effect of neridronate in the treatment of osteoporosis in postmenopausal women,<sup>22,23</sup>  $\beta$ -thalassemia patients,<sup>24</sup> osteoporotic patients with prostate cancer,<sup>25,26</sup> and patients after transplantation<sup>27</sup> to conduct a meta-analysis on the effect of neridronate in the treatment of osteoporosis.

## Materials and methods

### Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations were used to guide the present study. PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched for clinical trials with “neridronate” and “osteoporosis” as keywords. Studies published until August 31,

2021, were considered. The search was limited to studies on humans, with no language restrictions, and included articles published ahead of print. The search strategy for PubMed was: (“neridronate” [all fields] AND “osteoporosis” [all fields]) AND (randomized clinical trial [filter]). The search strategy for CENTRAL was: (neridronate in title abstract keyword AND osteoporosis in title abstract keyword – in trials (word variations were searched)). The reference lists of the identified publications were reviewed manually for additional relevant studies.

### Inclusion and exclusion criteria

The inclusion criteria were RCTs using neridronate to treat osteoporosis of any cause. The exclusion criteria were non-RCTs and trials using neridronate for the treatment of diseases other than osteoporosis.

### Assessment of risk of bias

Quality assessment and risk of bias evaluations of the selected studies were rated using the Cochrane Collaboration's tool for assessing risk of bias (The Cochrane Collaboration, London, UK), which includes 6 items for the ranking.<sup>28</sup>

### Measures of treatment effect

The changes in BMD (expressed as g/cm<sup>2</sup>) from baseline were selected as the core indicator, with 95% confidence intervals (95% CIs), and were calculated using the Review Manager (RevMan) v. 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark; <https://revman.cochrane.org/info>). Secondary endpoints, such as changes in serum C-telopeptide of collagen type I (sCTX) and bone alkaline phosphatase (ALP) levels were also collected for analysis, when available.

### GRADE

Grading of Recommendations, Assessment, Development, and Evaluations for the studies were performed using the GRADEpro website service (<https://www.gradepr.org/>).<sup>29</sup>

### Statistical analyses

The changes in BMD, calcium homeostasis and bone turnover markers were presented as mean  $\pm$  standard deviation (M  $\pm$  SD) from baseline. If the BMD changes were presented as mean (95% CI upper level and lower level), the transformation of the data was calculated to find the SD of the data with the RevMan Calculator (<https://training.cochrane.org/resource/revman-calculator>).<sup>30</sup> Data analysis and the forest plot chart were performed with RevMan v. 5.3 using the inverse variance statistical method

with the random-effects model. The subgroup analysis was employed to explore the potential sources of heterogeneity. Begg's test was utilized to analyze the risk of publication bias using Stata v. 12 software (StataCorp LLC, College Station, USA).

## Results

### Literature search

The flow diagram of our literature search is presented in Fig. 1. PubMed and CENTRAL databases were independently searched for clinical trials evaluating neridronate for the treatment of osteoporosis. Of the 42 retrieved reports, there were 28 records that required title/abstract screening. Six clinical trial studies were eligible for further analysis.

### Study characteristics

The characteristics of the 6 selected studies are summarized in Table 1. All the studies were performed in Italy. The sample sizes of the studies were relatively small (39–118 patients). The study subjects were young adults with  $\beta$ -thalassemia,<sup>24</sup> middle-aged patients needing organ transplantation,<sup>27</sup> osteoporotic patients with prostate cancer,<sup>25,26</sup> and elderly postmenopausal women.<sup>22,23</sup> One study used a neridronate dosage of 50 mg bimonthly,<sup>22</sup> 3 studies<sup>23,26,27</sup> used a dosage of 25 mg monthly, and 1 study used a dosage of 100 mg every 90 days.<sup>24</sup> Two studies<sup>22,24</sup> lasted 24 months, while the other studies<sup>23,25–27</sup> lasted 12 months. All of the studies were randomized and controlled (dosing with calcium and vitamin D). Giannini et al.<sup>27</sup> and Morabito et al.<sup>25</sup> used a double-blind method.

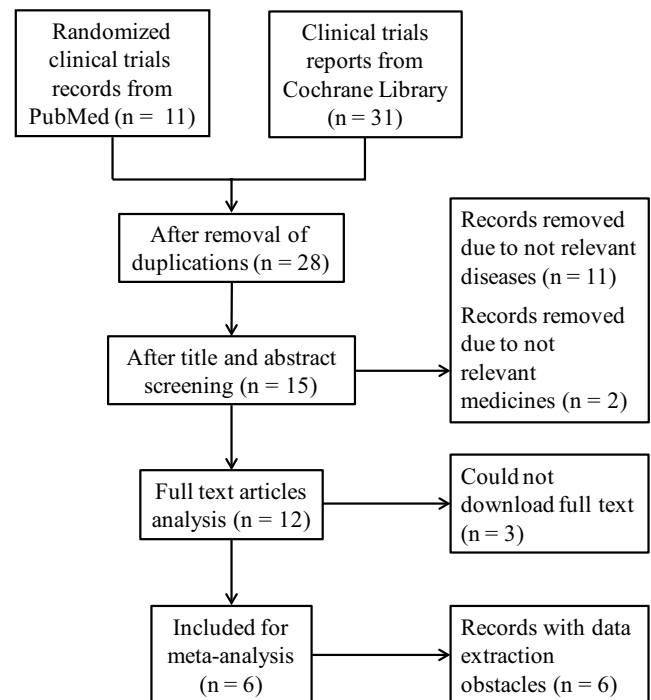


Fig. 1. Flow diagram of the search strategy and study selection process

### Assessment of risk of bias

The results of the risk of bias assessments are presented in Fig. 2. Four of the 6 selected studies were open-label studies, which resulted in uncertainty about the blinding methods.

### The effect of neridronate on BMD

Our pooled analysis showed that the administration of neridronate significantly increased the BMD compared

Table 1. Summary of analyzed studies with respect to study designs, medication and anthropometric assessment. All studies were conducted in Italy

Study	Disease	Study design	Dose	Duration [months]	Samples (n, neridronate)	Samples (n, control)	Co-intervention	Chelation therapy	Age [years]
Braga et al. <sup>22</sup> 2003	postmenopausal osteoporosis	randomized, open-label, controlled	50 mg i.v. for 2 months	24	39	39	calcium, vitamin D	not mentioned	64.6 ± 7.7
Casella et al. <sup>23</sup> 2005	postmenopausal osteoporosis	randomized, open-label, controlled	25 mg i.m. for 1 month	12	20	20	calcium, vitamin D	not mentioned	72.7 ± 5.2
Forni et al. <sup>24</sup> 2012	$\beta$ -thalassemia patients with osteoporosis	randomized, open-label, controlled	100 mg i.v. for 90 days	24	54	64	calcium, vitamin D	deferirpone	33.1 ± 8.8
Morabito et al. <sup>25</sup> 2004	osteoporotic patients with prostate cancer	randomized, double-blind, controlled	25 mg i.m. for 1 month	12	24	24	calcium, vitamin D	not mentioned	74.85 ± 4.1
Magno et al. <sup>26</sup> 2005	osteoporotic patients with prostate cancer	randomized, controlled	25 mg i.m. for 1 month	12	30	30	calcium, vitamin D6	not mentioned	73.4 (range: 68–80)
Giannini et al. <sup>27</sup> 2021	transplantation-related osteoporosis	randomized, double-blind, controlled	25 mg i.m. for 1 month	12	22	17	calcium, vitamin D	not mentioned	49.3 ± 9.1

i.v. – intravenously; i.m. – intramuscularly.

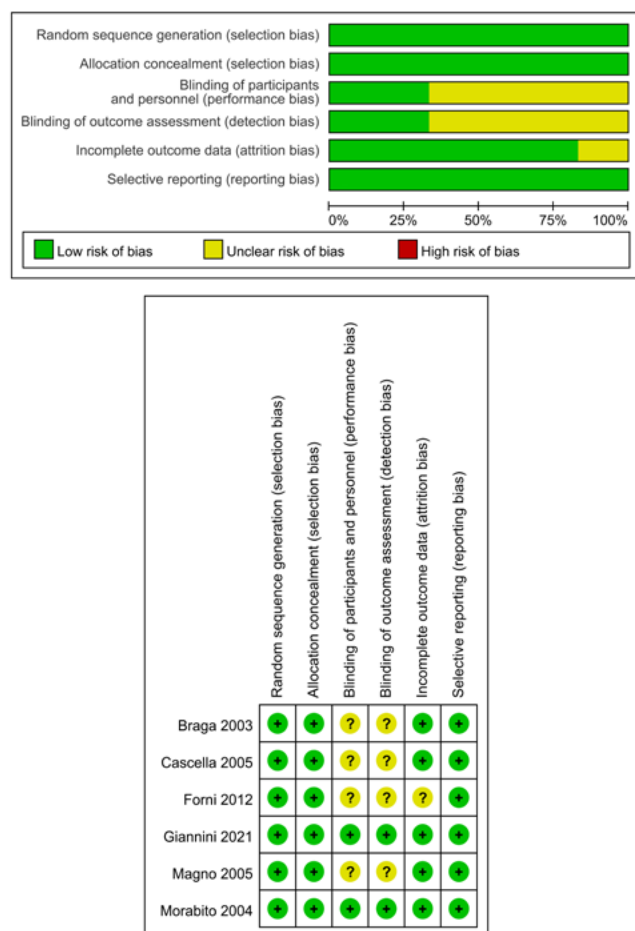


Fig. 2. Risk of bias of the selected studies

to using only calcium and vitamin D, which did not bring about significant improvements in BMD. Six studies<sup>22–27</sup> described an increase in the BMD of the lumbar spine (mean difference (MD) = 5.99, 95% CI: 3.96–8.02; Fig. 3A) and 5<sup>22–25,27</sup> reported BMD changes in the femoral neck (MD = 4.51, 95% CI: 2.01–7.01; Fig. 3B). Four studies<sup>24–27</sup> described changes in the BMD of the total hip (MD = 2.55, 95% CI: 2.10–3.00; Fig. 3C). The results of our pooled analysis suggested that neridronate administration can significantly increase the BMD of the lumbar spine, femoral neck and total hip in patients with osteoporosis, regardless of cause of the disease. The subgroup analysis indicated that greater improvement could be detected in patients with postmenopausal osteoporosis than in those with other causes of osteoporosis when evaluating BMD changes in the lumbar spine and femoral neck (Fig. 3A,B).

## The effect of neridronate on sCTX and bone ALP levels

Five of the 6 selected studies recorded a drastic decrease in sCTX and bone ALP level after neridronate administration. Significant decreases in sCTX (standardized mean difference (SMD) = -0.84, 95% CI: -1.32–-0.37; Fig. 4A) and ALP (MD = -5.29, 95% CI -7.31–-3.26, Fig. 4B) levels

after neridronate administration were detected at the end of the studies in our pooled analysis. The results suggested that neridronate can significantly reduce sCTX and bone ALP levels.

## GRADE

The certainty of evidence for all indicators was graded as high according to GRADE.

## Heterogeneity

The analysis of the effect of neridronate on BMD showed significant heterogeneity. A subgroup analysis was based on whether the subgroup approach using postmenopausal osteoporosis significantly reduced this heterogeneity.

## Publication bias

Results of Begg's test for each pooled analysis on the effect of neridronate on BMD indicated no evidence of publication bias (for lumbar spine:  $z = 0.64$ ,  $p = 0.520$ ; for femoral neck:  $z = 0.46$ ,  $p = 0.643$ ; for total hip:  $z = 0.34$ ,  $p = 0.734$ ; Fig. 5).

## Discussion

Over 200 million people are suffering from osteoporosis worldwide, with aging increasing the incidence rate.<sup>31</sup> It is estimated that 9 million cases of fractures occur due to osteoporosis each year.<sup>2</sup> Bisphosphonates, including alendronate and risedronate, are used as the first line of treatment for osteoporosis.<sup>32</sup> Neridronate is emerging as a potential treatment for several orthopedic diseases, including osteoporosis. This meta-analysis evaluated the efficacy of neridronate on patients with osteoporosis. Six RCTs were included in the analysis. The core indicator of the pharmacological effect were the patient's BMD changes in the lumbar spine, femoral neck and total hip. Secondary indicators were changes in sCTX and bone ALP levels. The GRADE analysis of the studies indicated a high degree of certainty for the evidence.

The main findings of our study are as follows. The administration of neridronate could significantly increase the BMD [ $\text{g}/\text{cm}^2$ ] of the lumbar spine (MD = 5.99, 95% CI: 3.96–8.02), femoral neck (MD = 4.51, 95% CI: 2.01–7.01) and total hip (MD = 2.55, 95% CI: 2.10–3.00) in patients with osteoporosis of all causes. The subgroup analysis indicated that a greater improvement could be detected in patients with postmenopausal osteoporosis than in those with the other causes of osteoporosis regarding BMD changes of the lumbar spine (postmenopausal osteoporosis (MD = 8.68, 95% CI: 7.33–10.02) as opposed to other causes (MD = 4.18, 95% CI: 3.27–5.09)) and femoral neck (postmenopausal osteoporosis (MD = 6.77, 95% CI: 5.56–7.99)

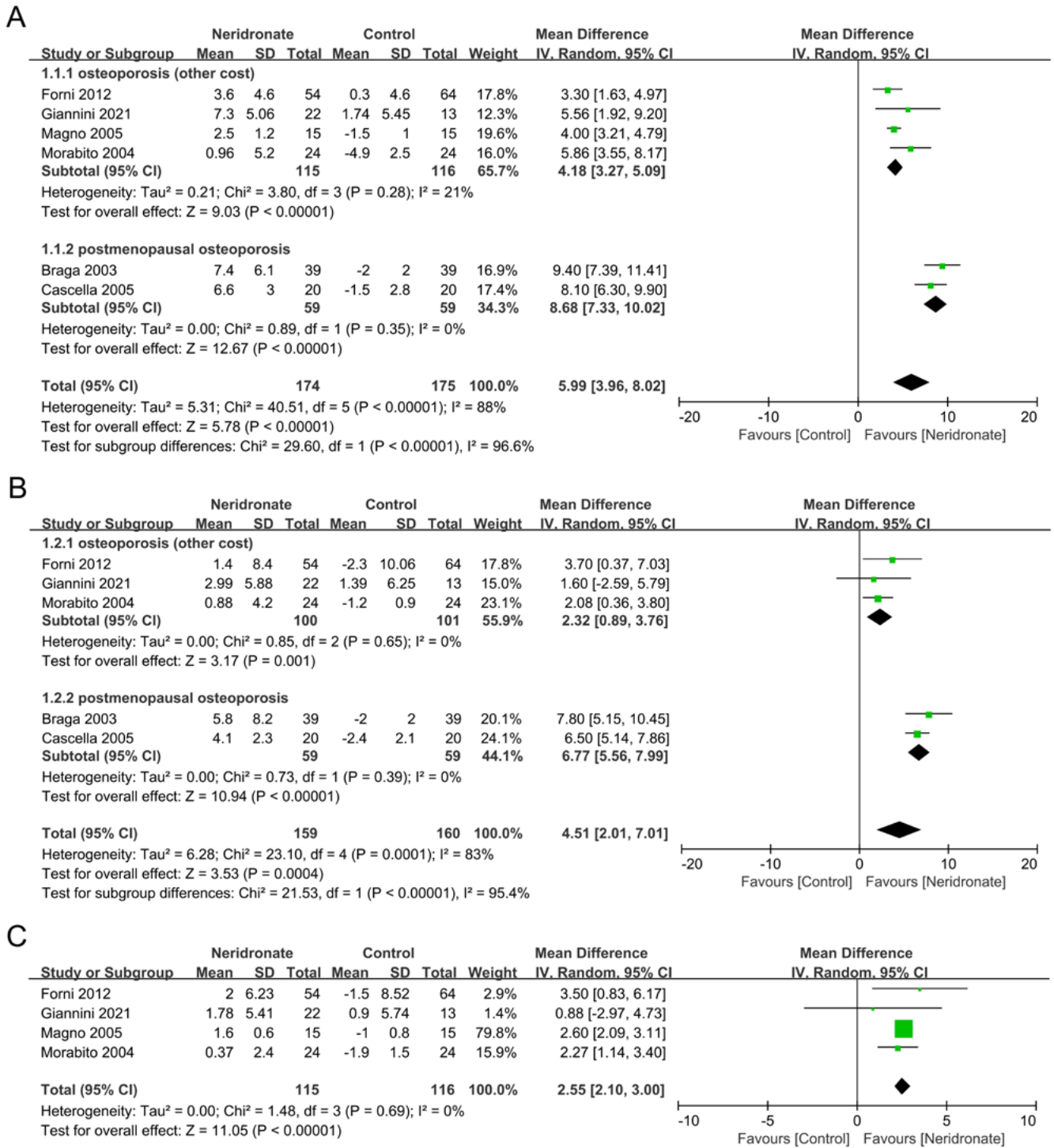


Fig. 3. A. Effect of neridronate on the bone mineral density (BMD) of the lumbar spine expressed as g/cm<sup>2</sup>; B. Effect of neridronate on the BMD of the femoral neck expressed as g/cm<sup>2</sup>; C. Effect of neridronate on the BMD of the total hip expressed as g/cm<sup>2</sup>

SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

compared to other causes (MD = 2.32, 95% CI: 0.89–3.76)). This suggests that neridronate brought about better BMD improvements in patients with postmenopausal osteoporosis than in those with osteoporosis resulting from other causes. Different effects of neridronate on the different types of osteoporosis generated high heterogeneity between the 2 subgroups (Fig. 3). However, the subgroup

analysis indicated low heterogeneity within the groups. The infusion of neridronate could also significantly reduce sCTX and bone ALP levels.

To our knowledge, this is the first meta-analysis to synthesize the effect of neridronate on BMD and other major indicators in patients with osteoporosis. Neridronate is a bisphosphonate that differs from other oral



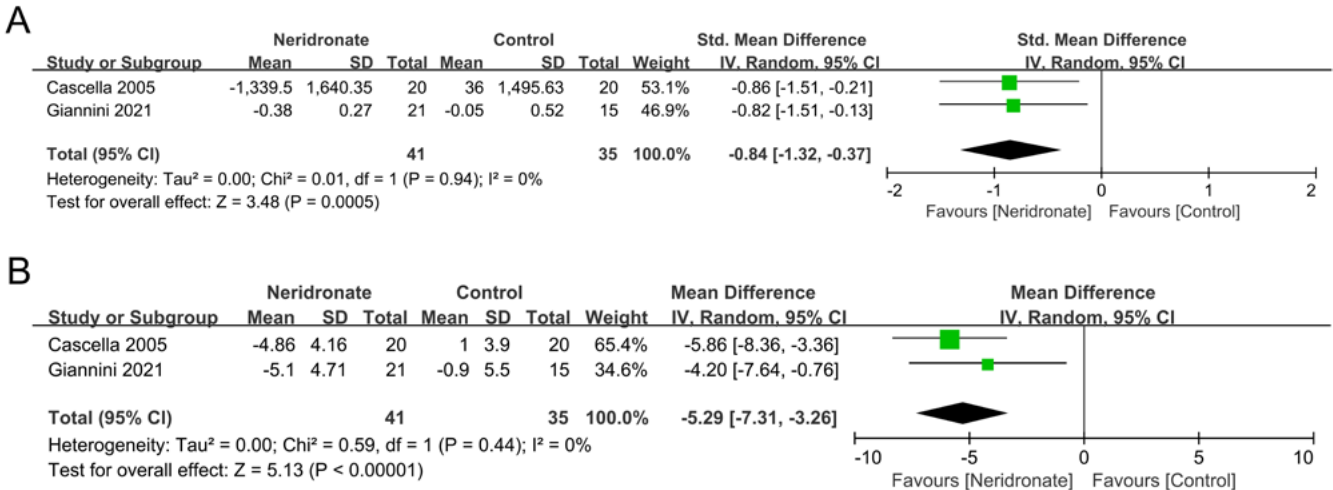


Fig. 4. A. Effect of neridronate on serum C-telopeptide of collagen type I (CTX); B. Effect of neridronate on bone alkaline phosphatase (ALP) concentration  
SD – standard deviation; 95% CI – 95% confidence interval; df – degrees of freedom.

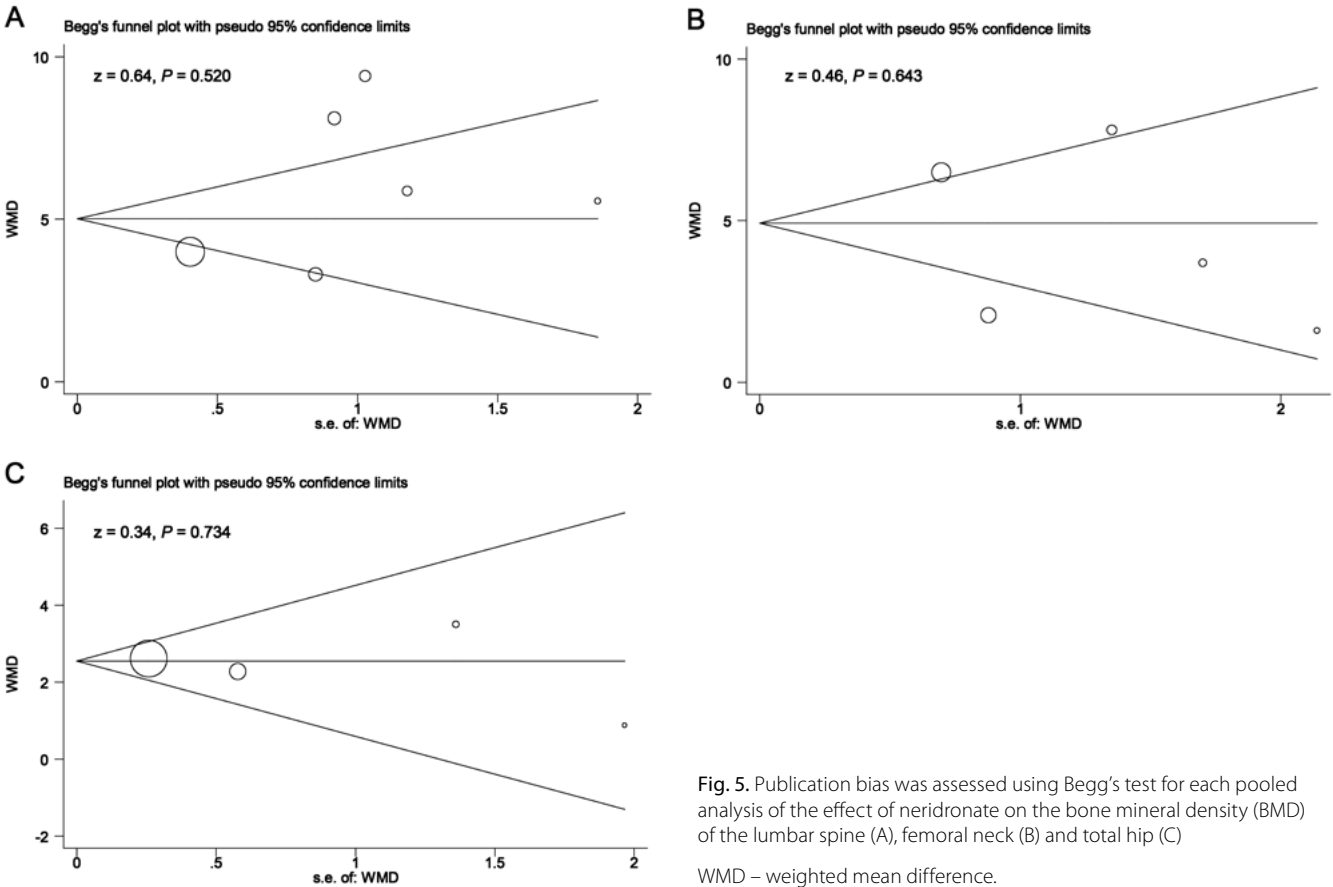


Fig. 5. Publication bias was assessed using Begg's test for each pooled analysis of the effect of neridronate on the bone mineral density (BMD) of the lumbar spine (A), femoral neck (B) and total hip (C)  
WMD – weighted mean difference.

bisphosphonates because it is administered by infusion. It has been approved in Italy for the treatment of osteogenesis imperfecta and Paget's disease. Adami et al. demonstrated that neridronate could significantly increase the BMD of the spine and total hip in a dose-dependent manner during a 12-month course of treatment.<sup>33</sup> Their study also reported a dose-dependent effect on sCTX and ALP levels, which is in accordance with our findings. In our analysis, neridronate brought about significant lumbar

spine and femoral neck BMD improvements in patients with postmenopausal osteoporosis. This finding is in line with a 6-year prospective study conducted by Guiducci et al.<sup>34</sup> Another study indicated that neridronate shares the same virtue as the other bisphosphonates of improving postmenopausal osteoporosis.<sup>35</sup> Besides the improvement of postmenopausal osteoporosis, neridronate could also modify the BMD of patients with osteoporosis resulting from other conditions. In our analysis, the BMD of the lumbar spine,

femoral neck and total hip was significantly improved in patients with prostate cancer,  $\beta$ -thalassemia and after transplantation. It is noteworthy that the effect of neridronate in patients with prostate cancer was to prevent bone loss instead of increasing BMD compared to placebo.<sup>25</sup> When applied to patients with  $\beta$ -thalassemia, neridronate led to a significant increase in BMD.<sup>24</sup> Similar findings were reported in a previous meta-analysis by Tsartsalis et al.<sup>7</sup> However, it was also reported that zoledronate had a better effect than neridronate with regard to improving the BMD of the lumbar spine in patients with  $\beta$ -thalassemia.<sup>7,36</sup> Organ transplantation can result in bone loss. Ho et al. analyzed 9 studies and found that using bisphosphonate after a liver transplant improves BMD and reduces fracture rates,<sup>37</sup> which is in line with the clinical trial results reported by Giannini et al.<sup>27</sup> They stated that neridronate improved BMD in patients after heart, lung and liver transplantation. The pooled analysis of this study indicated that neridronate infusion could significantly increase the BMD of the lumbar spine, femoral neck and total hip compared to a placebo in patients with postmenopausal osteoporosis, prostate cancer,  $\beta$ -thalassemia, and after transplantation. Neridronate infusions also provide benefits by significantly reducing bone turnover biomarkers such as sCTX and ALP levels. This is the basis for the BMD improvement of the medication and can be detected across the clinical trials where bisphosphonates were used.<sup>34</sup> Reduction in these biomarkers signifies a beneficial impact of neridronate on inhibiting osteoclast-mediated bone resorption, a key underlying mechanism in osteoporosis.

## Limitations

Although all the selected studies were RCTs, the samples were relatively small. Unfortunately, one RCT<sup>33</sup> was not included due to obstacles in data extraction. More studies are needed to verify the effect of neridronate on osteoporosis with causes other than being a postmenopausal woman. Since neridronate use is permitted only in Italy, the effect of the medication on patients of other nationalities could not be assessed. Finally, based on the current findings, more studies should be done to compare the effect of neridronate and other oral bisphosphonates in the treatment of osteoporosis.

## Conclusions

In summary, significant evidence has indicated that the long-term administration of neridronate could significantly increase the BMD of the lumbar spine, femoral neck and total hip in patients with postmenopausal osteoporosis and osteoporosis caused by prostate cancer,  $\beta$ -thalassemia and transplantation. It also decreases sCTX and ALP levels. These results are in accordance with previous findings that bisphosphonate medications,

including neridronate, can provide significant improvements in the treatment of osteoporosis. Hence, neridronate treatment offers a promising therapeutic intervention for the management of osteoporosis, particularly among patients with postmenopausal osteoporosis, thus providing hope for improved bone health.

## Availability of data and materials

The analyzed datasets generated during the study are available from the corresponding author upon reasonable request.

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