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Differences in union time, dash score and range of motion between giving bisphosphonate and without giving bisphosphonate of osteoporosis patients with distal radius fracture: a systematic review and meta-analysis

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ABSTRACT

Background: Osteoporosis is a common health problem. Meanwhile, the incidence of distal radius fracture increases with osteoporosis. The standard modality for osteoporosis is a combination of pharmacological therapy, one example of which is the administration of bisphosphonates. There is some disagreement about bisphosphonates' effect on the treatment of distal radius fractures in osteoporosis patients. This study aims to conclude the effect of bisphosphonates for this condition on both functional and radiological outcomes.

Methods: A systematic search was carried out on the PUBMED database and Google Scholar on studies comparing the timing of bone fusion, Disability of Arm, Shoulder, And Hand (DASH) scores, and wrist Range of Motion (ROM) among distal radius fracture patients with or without additional bisphosphonate therapy. A prospective or retrospective cohort study and a randomized controlled trial were included in this study during 2000-2020. Inclusion and exclusion criteria were used for sample selection. Weight Mean Difference (WMD) was used to assess the statistical results in RevMan version 5.3 for Windows.

Results: A search through the PUBMED and Google Scholar databases yielded 376 studies. Scanning titles and abstracts from studies that met the inclusion and exclusion criteria resulted in 6 articles. In total, there were 973 patients with distal radius fractures who received different treatment on bisphosphonate therapy. There was a significant difference in time to union with bisphosphonates (WMD=0.56; 95% CI=-0.94-2.06). Meanwhile, there was no significant difference in the assessment of DASH and ROM scores (WMD=0.27; 95% CI= -1.01-1.55).

Conclusion: Bisphosphonates provide a slower time to union in osteoporotic patients with distal radius fracture.

Keywords: Osteoporosis, Distal Radius Fractures, Union, Dash Score, Bisphosphonates.
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INTRODUCTION

Fractures caused by osteoporosis are a health problem that causes morbidity in fractures due to minor trauma and reduces the patient's quality of life. One of the fractures due to osteoporosis is the distal radius fracture.[1] This fracture is a pathological fracture that usually occurs the earliest, so it is widely used as a warning sign that the patient has osteoporosis.[1] Bisphosphonates act to inhibit osteoclasts that play a role in fracture healing, but on the other hand, these obstacles may also increase the density of the callus formed so that it may speed up the union.[2] Because of this controversy, a meta-analysis based on previous clinical trials was needed to determine the safety and effectiveness of bisphosphonates in distal radius fractures due to osteoporosis.

Osteoporosis is a generalized bone condition in which there is a combination of decreased bone matrix osteoblastic formation and increased osteoclastic bone resorption.[3] This combination makes bones brittle and has a high risk of fracture.[3] Osteoporosis is a common health problem in around 200 million people. All over the world suffer from this problem.[4] The clinical manifestations of osteoporosis can

Table 1. Studies included in the analysis.

Authors	Journal	Study Design	Level of Evidence
Rozental et al. (2009)	Journal of Hand Surgery	Retrospective Cohort	Level III
Gong et al. (2012)	The Journal of Bone and Joint Surgery	Prospective RCT	Level I
Uchiyama et al. (2013)	The Bone and Joint Journal	Prospective RCT	Level I
Seo et al. (2013)	Osteoporosis	Retrospective Cohort	Level III
Koshy et al. (2017)	Asian Journal of Pharmaceutical and Clinical Research	Prospective Non-RCT	Level II
Duckworth et al. (2019)	Journal of Bone and Mineral Research	Prospective RCT	Level I

Table 2. Critical assessments for each study used are based on the JBI form

No.	Validity	Rozental et al. (2009)	Gong et al. (2012)	Uchiyama et al. (2013)	Seo et al (2013)	Koshy et al (2017)	Duckworth et al. (2019)
1	Are the two groups similar and drawn from the same population?	Yes	Yes	Yes	Yes	Yes	Yes
2	Is exposure measured in 1 the same way as to assign people to the exposed and non-exposed groups?	Yes	Yes	Yes	Yes	No	Yes
3	Is exposure measured in a valid and reliable manner?	Yes	Yes	Yes	Yes	Yes	Yes
4	Are confounding factors identified?	Yes	Yes	Yes	Not Clear	Yes	Yes
5	Are strategies for dealing with confounding factors described?	Not Clear	Yes	Yes	Not Clear	Yes	Yes
6	Was the group/participant independent of the results at the start of the study (or at the time of presentation)?	Yes	Yes	Yes	Yes	Yes	Yes
7	Are the results measured in a valid and reliable way?	Yes	Yes	Yes	Yes	Yes	Yes
8	Is follow-up time reported and long enough to produce results?	Yes	Yes	Yes	Yes	Yes	Yes
9	Is follow-up complete, and if not, are the reasons for loss to follow-up explained and explored?	Yes	Yes	Yes	Yes	Yes	Yes
10	Are strategies for dealing with the incomplete follow-up being used?	Yes	Yes	Yes	Yes	Yes	Yes
11	Is appropriate statistical analysis used?	Yes	Yes	Yes	Yes	Yes	Yes

include pain, susceptibility to fractures, and physical disability leading to loss of independence and long-term care.[4]

Due to this controversy, and because until now there has been no meta-analysis that describes the effect of bisphosphonates on the healing of distal radius fragility fractures and the results vary widely between studies, a meta-analysis is needed to draw conclusive and objective conclusions regarding the effect of bisphosphonates. for this condition. With our meta-analysis, we hope that it can be considered for administering bisphosphonates to patients with distal radius fragility fractures so that the management of fragility fracture patients due to osteoporosis will be better the morbidity rate can also be reduced.

MATERIALS AND METHODS

The study design used was the meta-analysis method, a systematic search was carried out on the PubMed and Google Scholar databases to identify and find studies comparing the time to union, Disability Scores of Arm, Shoulder, and Hand (DASH), as well as the Range of Motion (ROM) which includes ROM supination, pronation, flexion, extension, radial deviation, and ulnar deviation of the wrist among distal radius fracture patients with additional bisphosphonate therapy without additional bisphosphonate therapy published from 1994 to October

Table 3. General characteristics from literature in this study

Reference	Total Subjects	Treatment (n=973)		Intervention (N=973)		Bisphosphonate Types and Administration
		Conservative (n=502) (%)	Operative (N=471) (%)	DB (N=446) (%)	TB (N=527) (%)	
Rozental et al. (2009)	196	109 (55.60)[a]	87 (44.40)[b]	43 (21.90)	153 (78.10)	Alendronate in 37 (86%) patients and Risedronate in 6 (14%) patients
Gong et al. (2012)	50	0 (0.00)	50 (100.00)[c]	24 (48.00)	40 (52.00)	Alendronate 70 mg once/week
Uchiyama et al. (2013)	80	0 (0.00)	80 (100.00)[d]	40 (50.00)	40 (50.00)	Alendronate 35 mg once/week (Oral)
Seo et al. (2013)	160	0 (0.00)	160 (100.00)[e]	33 (56.10)	33 (43.10)	Alendronate 5 mg per oral and Zolendronate 5 mg / 100 ml IV
Koshy et al. (2017)	66	66 (100.00)	0 (0.00)	33 (50.00)	33 (50.00)	TAD
Duckworth et al. (2019)	421	327 (77.70)[a]	94 (44.40)[f]	153(51.00)	2016(49.00)	Alendronate 70 mg once/week per oral

DB=conservative and/or operative therapy with additional bisphosphonate therapy; TB=conservative and/or operative therapy without additional bisphosphonate therapy; ORIF = open reduction and internal fixation; OREF = open reduction and external fixation, CRPP = closed reduction and percutaneous pinning, SD = standard deviation, TAD = no data; a=Cast; b=ORIF (14), OREF (1), ORIF and OREF (2), and CRPP (1); c= ORIF (volar plate fixation); d= ORIF (volar locking plate and screws); e= ORIF (*plate fixation*); f= ORIF (67), OREF (17), and CRPP (10)

Table 4. Outputs assessed in the meta-analysis (Mean±SD) regarding union time, Dash Score, ROM Supine, and ROM Prone.

Reference	Union Time (Days)		Dash Score			ROM Supine		ROM Prone	
	DB	TB	DB	TB	Evaluation Time	DB	TB	DB	TB
Rozental et al. (2009)	55.00±17.00	49±14	TAD	TAD	TAD	TAD	TAD	TAD	TAD
Gong et al. (2012)	46.90±10.50	47,6 ± 11,2	17,0±14,0	15,0±14,0	24 weeks postoperative	74.00±13.00	77.00±9.00	66.00±12.00	65.00±12.00
Uchiyama et al. (2013)	102.00±4.20	102 ± 3.9	TAD	TAD	TAD	TAD	TAD	TAD	TAD
Seo et al. (2013)	47.60±14.00 (PO)	46,9 ± 23,1	16,7 ± 5,0	15,7±5,3	24 weeks	74.30 ± 7.40	72.70±4.90	74.20±7.40	71.40±7.20
	49.70±14.70 (IV)	46,9 ± 23,1	16,9 ± 8,0	15,7±5,3	postoperative	72.60 ± 7.30	72.70±4.90	73.20±9.30	71.40±7.20
Koshet et al. (2017)	50.90±12.60	50,9 ± 14,0	25,2 ± 7,6	28,8±8,4	6 weeks postoperative.	58.60 ± 12.30	54.10± 11.90	45.60±13.00	42.50±13.00
			48,9±17,4	49,8±18,1	2 weeks postoperative				
Duckworet et al. (2019)	TAD	TAD	25,7±16,9	25,4±20,2	8 weeks postoperative	TAD	TAD	TAD	TAD
			12,7±14,7	13,3±16,0	26 weeks postoperative				

DB=conservative and/or operative therapy with additional bisphosphonate therapy; TB=conservative and/or operative therapy without additional bisphosphonate therapy; DASH=disability of arm shoulder and hand; ROM=range of motion; TAD=no data; PO=Per Oral; IV=Intravenous

Table 5. Outputs assessed in the meta-analysis (Mean±SD) regarding ROM Flexy, Rom Extension, Radial Deviation, and Ulnar Deviation ROM

Reference	ROM Flexy		ROM Extension		Radial Deviation ROM		Ulnar Deviation ROM	
	DB	TB	DB	TB	DB	TB	DB	TB
Rozental et al (2009)	TAD	TAD	TAD	TAD	TAD	TAD	TAD	TAD
Gong et al (2012)	50.00±10.00	51.00±14.00	64.00±10.00	66.00±10.00	TAD	TAD	TAD	TAD
Uchiyama et al (2013)	TAD	TAD	TAD	TAD	TAD	TAD	TAD	TAD
Seo et al (2013)	59.60±5.30 (PO)	59.50±4.80	65.00±4.40	65.40±3.70	20.30±3.30	21.20±3.50	29.50±4.50	30.00±4.20
	60.00±7.00 (IV)	59.50±4.80	63.90±7.80	65.40±3.70	20.30±3.40	21.20±3.50	29.90±5.60	30.00±4.20
Koshy et al. (2017)	60.00±12.40	58.80±10.50	49.10±11.60	48.90±10.70	12.30±5.70	12.30±5.20	20.60±6.30	19.40±6.30
Duckworth et al. (2019)	TAD	TAD	TAD	TAD	TAD	TAD	TAD	TAD

DB=conservative and/or operative therapy with additional bisphosphonate therapy; TB=conservative and/or operative therapy without additional bisphosphonate therapy; DASH=disability of arm shoulder and hand; ROM=range of motion; TAD=no data; PO=Per Oral; IV=Intravenous

2020 The search strategy was to use keywords such as "distal radius fracture" and "bisphosphonates" and "outcome". Only human studies in the form of a full manuscript (full version) were included in the study.

Inclusion criteria included patients older than 45 years diagnosed with a fracture of the distal radius. Randomized control studies, cohorts, and retrospective studies were included in this study, while case series and case reports were excluded. The effectiveness comparison is based on the time to union in hours, DASH, and ROM, including supination, pronation, flexion, extension, radial deviation, and ulnar deviation of the wrist in degrees. The study sample consisted of all articles in PubMed and/or Google Scholar comparing the time to union, DASH, and ROM, which includes supination, pronation, flexion, extension, radial deviation, and ulnar deviation of the wrist among patients with distal radius

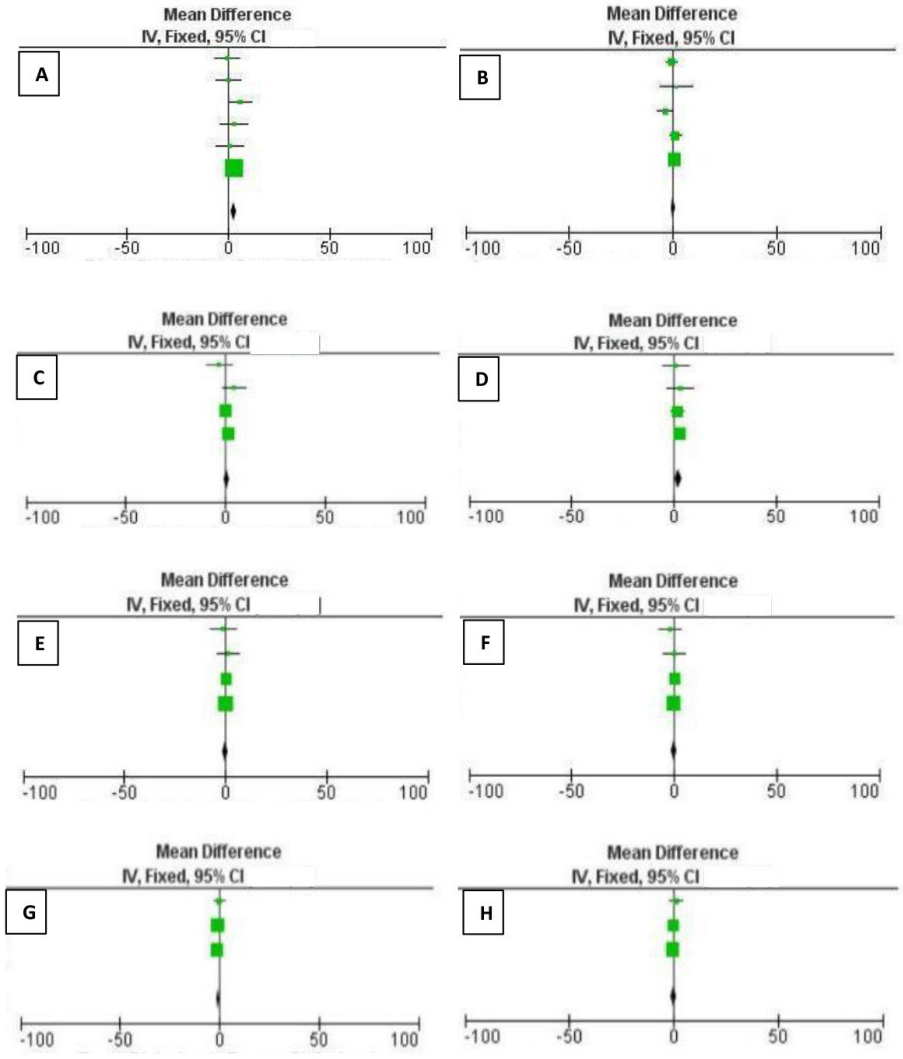

Figure 1. The analysis results (forest plot) of the (A) union time variable (Days), (B) the variable DASH score; (C) supination ROM variable (degree); (D) pronation ROM variable (degree); (E) flexion ROM variable (degree); (F) extension ROM variable (degree); (G) radial deviation ROM variable (degree); and (H) ulnar deviation ROM variable (degree).

fracture with additional bisphosphonate therapy with no added bisphosphonate therapy were published from 1994 to October 2020, which met the inclusion and exclusion criteria.

Where exclusion criteria included animal studies, patients with a follow - up of less than 3 weeks, patients with congenital abnormalities, patients with pathological fractures due to tumors or infections, patients with open fractures and neurovascular disorders at baseline, recurrent fractures, fractures that failed in reduction, multiple trauma, patients with surgery more than 3 weeks after the fracture which may require osteotomy and patients with conditions capable of affecting bone mineral density such as kidney or adrenal gland disorders, diabetes, rheumatoid arthritis, thyroid disease, Parkinson's disease, pulmonary obstruction chronic, autoimmune disease or a history of use of drugs that affect bone mineral density, such as corticosteroids, as well as patients with dementia or other psychiatric disorders and patients who refuse to participate.

A thorough search through the PubMed database found 12 articles, while the Google Scholar database found 364 articles, so that overall, from the two databases, we obtained 376 articles. Through a screening process based on titles and abstracts, 9 articles were obtained that were relevant to the issues discussed. Articles were then excluded again based on inclusion and exclusion criteria in full-text filtering and by looking at the data's completeness so that 6 articles were obtained in the systematic study. The articles received consist of 3 articles of the prospective randomized clinical trial (evidence level I), 1 article prospective non-randomized clinical trial (evidence level II), and 2 articles of the retrospective cohort (evidence level III). Meta-analysis was conducted using RevMan version 5.3 for Windows.

RESULTS

The PubMed database's search process got 12 articles and a search on the Google Scholar database got 364 articles. The screening process resulted in 6 articles that were included in the systematic study. The articles obtained consist of 3 articles of the prospective randomized clinical trial (evidence level I), 1 article prospective non-randomized clinical trial (evidence level II), and 2 articles of the retrospective cohort (evidence level III), which can be seen in Table 1. Critical study The 6 studies used were based on the Joanna Briggs Institute (JBI) scoring system, which showed no study with more than 3 parameters was invalid (Table 2).

The bisphosphonate regimen administered to the treatment group included oral alendronate and risedronate and intravenous zolendronate. The conservative treatment given is the immobilization of a cast. At the same time, operative management includes open reduction and internal fixation (ORIF), open reduction and external fixation (OREF), or closed reduction and percutaneous pinning (CRPP) (Table 3). The analyzed outputs included time union, disability score of arm, shoulder, and hand (DASH) and range of motion (ROM) listed in Table 4. The ROM assessed in Table 4 included supine and prone. Besides, Table 5 depicted the ROM flexy, extension, radial deviation, and ulnar deviation.

Data were obtained from five studies that were included in the analysis process

for the variable union time. The total number of subjects was 621 patients consisting of 231 (37.2%) patients who received additional bisphosphonate therapy and 390 (62.8%) patients without additional bisphosphonate therapy.[5–9] For the union time variable's meta-analysis process, a fixed-effect model is used for the output in the form of continuous numeric data. The analysis results and the Forest plot in Figure 1 show a significant difference in the mean-time of union between the two groups, with the bisphosphonate group showing a prolonged union time compared to the group without bisphosphonates. (heterogeneity I2 = 0% with p-value heterogeneity = 0.46; WMD = 0.56; Confidence Interval (CI) 95% = -0.94 - 2.06; and p-value = 0.46) (Figure 1).

For the DASH score variable, data were obtained from four studies included in the analysis process. The total number of subjects was 766 patients consisting of 363 (47.4%) patients who received additional bisphosphonate therapy and 403 (52.6%) patients without additional bisphosphonate therapy.[6,8-10] For the DASH score variable's meta-analysis process, a fixed-effect model is used for the output in the form of continuous numeric data. The results of the analysis and Forest plot in Figure 3 show that there is no significant difference in the mean DASH score between the two groups (heterogeneity I2 = 26% with p-value heterogeneity = 0.25; WMD = 0.27; Confidence Interval (CI) 95% = -1.01 - 1.55; and p-value = 0.68) (Figure 1).

For the ROM supination variable, data were obtained from three studies that were included in the analysis process, namely data from Gong et al., Koshy et al., and Seo et al. The total number of subjects was 345 patients consisting of 148 (42.9%) patients who received additional bisphosphonate therapy and 197 (57.1%) patients without additional bisphosphonate therapy. Effect model for output in the form of continuous numeric data. The results of the analysis and Forest plot in Figure 4 show that there is no significant difference in the mean angle of ROM supination between the two groups (heterogeneity I2 = 23% with p-value heterogeneity = 0.27; WMD = 0.76; 95% CI = -0.83 - 4.07; and p-value = 0.35) (Figure 1).

For the pronation ROM variable, data were obtained from three studies included in the analysis process. The total number of subjects was 345 patients consisting of 148 (42.9%) patients who received additional bisphosphonate therapy and 197 (57.1%) patients without additional bisphosphonate therapy.[6,8,9] For the meta-analysis process of pronation ROM angle variables, a fixed-effect model is used for the output in the form of continuous numeric data. The results of the analysis and Forest plot in Figure 5 show that there is a significant difference in the mean pronation ROM angle between the two groups where the mean pronation ROM angle is significantly greater in the group receiving bisphosphonate therapy compared to those who do not receive bisphosphonate therapy (heterogeneity I2 = 0 % with p-value heterogeneity = 0.93; WMD = 2.32; 95% CI = 0.43 - 4.22; and p-value = 0.02) (Figure 1).

For the flexion ROM variable, data were obtained from three studies included in the analysis process. The total number of subjects was 345 patients consisting of 148 (42.9%) patients who received additional bisphosphonate therapy and 197 (57.1%) patients without additional bisphosphonate therapy.[6,8,9] For the meta-analysis process of flexion ROM angle variables, a fixed-effect model is used for the output in the form of continuous numerical data. The results of the analysis and Forest plot in Figure 6 show that there is no significant difference in the mean ROM flexion angle between the two groups (heterogeneity I2 = 0% with p-value heterogeneity = 0.96; WMD = 0.27; 95% CI = -1.13 - 1.67; and p-value = 0.71) (Figure 1).

For the extension ROM variable, data were obtained from three studies that will enter the analysis process. The total number of subjects was 345 patients consisting of 148 (42.9%) patients who received additional bisphosphonate therapy and 197 (57.1%) patients without additional bisphosphonate therapy.[6,8,9] For the meta-analysis process of extension ROM angle variables, a fixed-effect model is used for output in the form of continuous numerical data. The results of the analysis and Forest plot in Figure 7 show that there is no significant difference in the mean angle of ROM extension between the two groups (heterogeneity I2 = 0% with p-value heterogeneity = 0.88; WMD = 0.12; 95% CI = -1.26 - 1.50; and p-value = 0.86) (Figure 1).

For the radial deviation ROM variable, data obtained from two studies that will be included in the analysis process, the total number of subjects was 295 patients consisting of 124 (42.0%) patients who received additional bisphosphonate therapy and 171 (58.0%) patients without additional therapy. bisphosphonates.[8,9] For the meta-analysis process of radial deviation ROM angle variables, a fixed-effect model is used for output in the form of continuous numerical data. The results of the analysis and the Forest plot in Figure 8 show that there is no significant difference in the mean radial deviation ROM angle between the two groups (heterogeneity I2 = 0% with p-value heterogeneity = 0.40; WMD = -0.81; Confidence Interval (CI)) 95% = -1.66 - 0.05; and p-value = 0.06) (Figure 1).

For the ulnar deviation ROM variable, data were obtained from two studies that will enter the analysis process. The total number of subjects was 295 patients consisting of 124 (42.0%) patients who received additional bisphosphonate therapy and 171 (58.0%) patients without additional therapy bisphosphonates.[8,9] For the meta-analysis process of the ulnar deviation ROM angle variable, a fixed-effect model was used for the output in the form of continuous numeric data. The results of the analysis and Forest plot in Figure 9 show that there is no significant difference in the mean ulnar deviation ROM angle between the two groups (heterogeneity I2 = 0% with p-value heterogeneity = 0.63; WMD = -0.11; Confidence Interval (CI)) 95% = -1.26 - 1.05; and p-value = 0.86) (Figure 1).

DISCUSSION

From the results of data collection, it can be concluded that the level of evidence of this research is good enough. We can get 3 studies with evidence level I. From the total study, a total of 973 patients were obtained. Duckworth et al., used a prospective randomized clinical trial study technique with a total of 421 patients who received different treatment

on bisphosphonate therapy.[10] Uchiyama et al. used the prospective randomized clinical trial type of study with patients receiving therapy. Operative treatment for distal radius fractures and divided into two groups on bisphosphonate therapy.[5] While Gong et al., with a total of 50 patients conducted a study regarding the administration of alendronate therapy 70 mg once a week after undergoing ORIF surgery for distal radius fractures.[6]

In the analysis of bone union time in distal radius fractures, there was a significant difference between the group with bisphosphonate therapy and the group without bisphosphonate therapy where the group's union time with bisphosphonate therapy was prolonged compared to the group without bisphosphonate. This is consistent with a systematic review that concluded that bisphosphonates show a significant lengthening of union time for fractures of the distal radius.

In the study of DASH scores, data from four studies showed no significant difference between the two treatment groups with a Confidence Interval (CI) of 95% = -1.01 - 1.55; and p-value = 0. This increased DASH value is in line with the study conducted by Gong et al and Seo et al. that the group that received bisphosphonate therapy got a higher DASH score than the group that did not receive bisphosphonates.[6,8]

The results of ROM analysis studies in the bisphosphonate therapy group were carried out by several analyzes of ROM supination, pronation, flexion, extension, radial deviation, and deviation of the ulna at the wrist. In general, the results were not significant in the entire ROM of patients after receiving bisphosphonate therapy compared to the group that did not receive bisphosphonate therapy. Only a significant increase in pronation ROM was found. This may be due to the resting position of the arms and hands in the pronation position. But other types of ROM such as supination, flexion, extension, radial deviation, ulnar deviation did not increase significantly, which was consistent with the absence of a significant DASH score. Accordingly, Seo et al. stated that at 24 weeks, there was no significant increase in ROM on the evaluation of ROM dorsiflexion, palmar-flexion, radial deviation, ulnar deviation, supination, and also pronation.[8] Research by Gong et al. and Koshy et al. also found no improvement. ROM was significant in both treatment groups.[6,9]

CONCLUSION

In addition to bisphosphonate therapy compared without additional bisphosphonate therapy in osteoporosis patients with distal radius fractures, there was a significant difference in bone fusion time. Still, there was no significant difference in DASH scores. In the Range of Motion (ROM) wrist pronation, there was a significant difference, but there was no difference in Range of Motion (ROM) supination, flexion, extension, radial deviation, and ulnar deviation of the wrist, which were significant in the addition of bisphosphonate therapy compared without the addition of bisphosphonate therapy on osteoporotic patients with distal radius fractures.

CONFLICTS OF INTEREST

The author states that there are no conflicts of interest regarding the material discussed in the manuscript.

RESEARCH ETHICS

The research protocol for Ethical Clearance from the Research Ethics Commission of the Medical Faculty of UNUD/Sanglah Hospital Denpasar will be submitted before the research is carried out. Subjects who met the research criteria were explained the research objectives and asked to fill out the informed consent. Researchers have also attached a secondary data collection permit in the form of medical records at Sanglah Hospital, Denpasar.

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AUTHOR CONTRIBUTION

Dwiwahyonokusuma is responsible for finding research samples, carrying out actions, analyzing data, and reporting research results. Putu Astawa is in charge of the research concept design and is the supervisor in this research.

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