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A randomized clinical trial on improving osteopenia in postmenopausal women after two years of preventive treatment with alendronate; a dose of 35 mg per week is more effective or a dose of 70 mg?

Mansoor Karimifar¹, Negar Botlani¹, Amirhossein Salari²

¹Departments of Rheumatology, Isfahan University of Medical Sciences Isfahan, Iran

²Rheumatology Research Center, Tehran University of Medical Sciences, Tehran, Iran

Correspondence to:

Negar Botlani, Email:
negarbotlani@gmail.com

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Abstract

Introduction: Osteoporosis is the most common metabolic bone disease worldwide. In this disease, the bone mass decreases and as it progresses, the risk of fracture increases. Osteopenia occurs in the early stages of bone loss. Studies on the effective dose for treatment of osteopenia have been controversial.

Objectives: In this randomized clinical trial, low doses versus high doses of alendronate were assessed during the osteopenic stage in postmenopausal women.

Patients and Methods: The present study is a randomized clinical trial (RCT) that was performed on 152 postmenopausal women who were visited in Al-Zahra rheumatology clinic between 2016 and 2017. Patients were randomly divided into two groups. The first group with 35 and the second group with 70 mg of weekly alendronate were treated and followed for two years. Densitometry was performed on patients before and 2 years after the intervention, and the findings were compared.

Results: The two groups were not significantly different in terms of age, gender, height, weight, body mass index (BMI) and menopause ($P > 0.05$). The bone mineral density (BMD) findings of both groups, including Fracture Risk Assessment Tool (FRAX) hip and vertebra/wrist, T-score hip and vertebrae, as well as Z-score hip and vertebrae, improved significantly after two years ($P < 0.001$). However, a comparison of the two therapeutic doses did not show a significant difference in terms of BMD improvements ($P > 0.05$).

Conclusion: The findings of this study reported favorable results for the preventive treatment of alendronate in osteopenic women. In addition, due to gastrointestinal problems that are the main complaint of alendronate use, according to the results, a weekly dose of 35 mg can be recommended.

Trial registration: The trial protocol was approved in the Iranian Registry of Clinical Trials (identifier: IRCT20190325043111N1; <https://www.irct.ir/trial/43014>, ethical code; IR.MUI.REC.1396.3.639.

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Introduction

Osteoporosis is the most common metabolic bone disease worldwide, known to be based on low bone mass and worsening bone tissue status. When this process progresses, it increases the risk of pathological fractures (1). The rate of osteoporotic fractures in the Iranian population is increasing rapidly, especially with increasing population trend (2). Osteoporotic fractures around the world are associated with very high morbidity and mortality, and place a very heavy economic burden on the health care system of the community (3,4). Therefore, prevention of osteoporotic fractures in the elderly in addition to the morbidity of the disease, in terms of economic burden on the health system is of particular importance (5,6).

So far, the treatment of osteoporosis

Key point

In a randomized clinical trial to improve osteopenia in postmenopausal women after two years of preventive treatment with 35 mg alendronate versus 70 mg, we found the preventive treatment of alendronate in osteopenic women. In addition, due to gastrointestinal problems that are the main complaint of alendronate use, according to the results, a weekly dose of 35 mg can be recommended.

has been extensively evaluated using bisphosphonate compounds, especially alendronate, while information on the prophylactic treatment of postmenopausal women with osteopenia rather than osteoporosis is still in question (7,8).

A study in Europe evaluated the cost-effectiveness of alendronate in osteopenic conditions in postmenopausal women with no history of pathological fractures.



They found, the value of such treatment depends on the country, the tendency to premature treatment, as well as the discount rate (9). Another study in the United States found that treatment with alendronate in postmenopausal women had no preventive value on the occurrence of pathological fractures (10). A guideline, published in Japan, recommends preventive treatment in postmenopausal women, if there is a family history of osteoporotic hip fracture or Fracture Risk Assessment Tool (FRAX) indicates a 10-year fracture probability of at least 15% for major fractures (11).

Meanwhile, the latest guideline published in Europe by Kanis et al showed that drug treatment should be considered in patients having osteopenia when FRAX indicates a 10-year fracture probability of at least 20% for major fractures (12).

Objectives

Due to the lack of information about the effectiveness and dosage required for the treatment of osteopenia in postmenopausal women in Iranian society, treatment with alendronate was evaluated.

Patients and Methods

Study design

The present study is a randomized clinical trial (RCT) that was conducted on 152 postmenopausal women who were visited in Al-Zahra rheumatology clinic (between 2016 and 2017). Patients were randomly divided into

two groups. The first group was treated with 35 and the second group received 70 mg of weekly alendronate and followed for two years. Densitometry was performed for patients before and two years after the intervention, then the findings were compared (Figure 1).

Menopausal women with osteopenia (T-score between -1 up to -2.5 in any hip or spine) for primary reasons (such as decreased estrogen levels following menopause) or secondary (such as collagen-vascular diseases that require long-term treatment with corticosteroids), with normal serum levels of vitamin D, calcium, phosphorus, albumin, and alkaline phosphatase, without previous history of severe pathological or traumatic fractures and without symptoms or diagnosis of malignancy, entered to the study.

People who did not cooperate in determining the FRAX index for any reason, dissatisfaction to participate in the study, failure to complete the course of treatment with alendronate, and lack of referral for densitometry, all dropped out of the study.

After the study protocol was approved by the ethics committee of the university, the necessary information about the study process was explained to the patients and they were asked to sign a conscious consent form to attend the study.

Patient demographic data and their medication were included in a checklist. Due to the importance of steroids in bone density, steroid use was recorded as a risk factor for osteoporosis. Steroid administration was conditionally

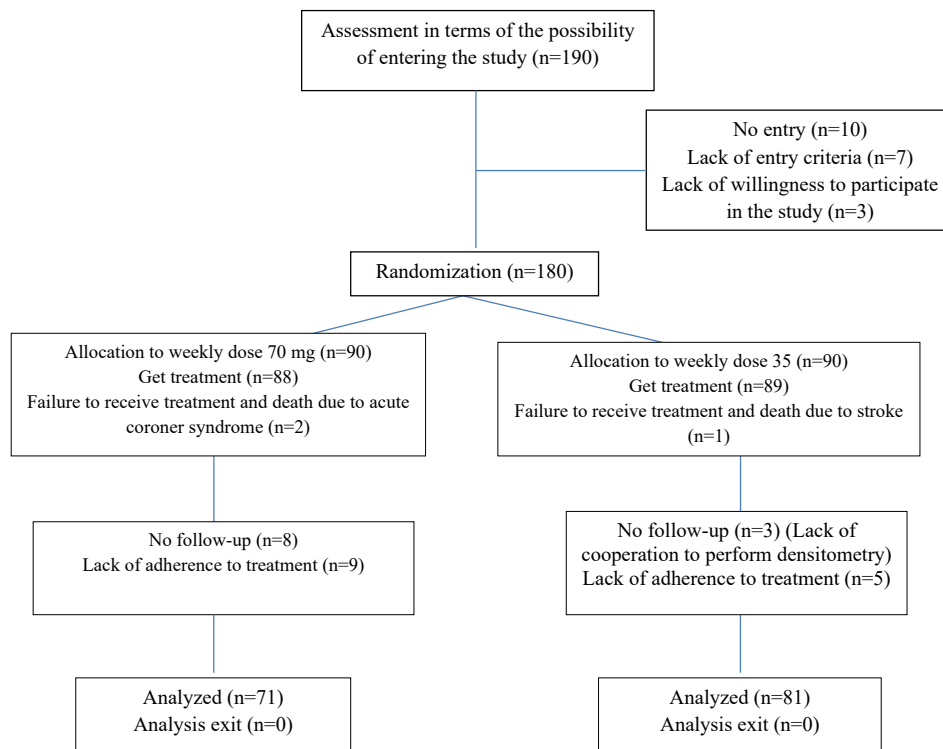


Figure 1. Flow chart of enrollment and allocation of participants and study design (Consort).

included in the checklist if the patient received 5 mg/day of prednisolone for three months or other steroids with dose adjustment according to the dose affecting bone density. Additionally, patients' height and weight were measured and their body mass index (BMI) was calculated. Patients were also asked about menopause onset and were listed on the study checklist. Steroid administration has been shown to be positive for those who have received at least 5 mg/day of prednisolone or another steroid equivalent for three months or more. Menopausal women who had osteopenia (a T-score between -1 up to -2.5 in the hip or spine) based on bone densitometry (Hologic, Explorer 2006, USA) were randomly assigned to be divided into two groups. The number of patients was determined based on the census, to reach the desired level. Patients were then divided into two groups based on the numbers provided by Random Allocation software. Thus, patients with individual numbers were treated with a weekly dose of 35 mg/alendronate (Osteofos; CIPLA; India) and group two patients were treated weekly with a dose of 70 mg/alendronate (Osteofos; CIPLA; India). Patients were treated for two years and their adherence to treatment was assessed during regular visits to the rheumatologist as well as repeated phone calls. Patients were contacted on a weekly basis and on the appointed day by telephone, and were asked about medication. In this study, the rheumatologist who evaluating the patients was blinded to their treatment group and the study checklists were completed by two project managers. Therefore, the rheumatologist cooperated in examining patients and interpreting densitometric findings. Bone mineral density (BMD) was taken from all patients after two years, and T-score, Z-score for hip and spine were re-evaluated, and FRAX was determined. In the present study, the FRAX and BMD findings were defined as risk factors for fracture. Then, changes in these findings were compared to evaluate the effect of alendronate at two doses of 35 and 70 mg/wk (12).

Ethical issues

The research was conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (#IR.MUI.REC.1396.3.639). The institutional ethical committee at Isfahan University of Medical Sciences accepted all study protocols. Accordingly, written informed consent was taken from all participants before any intervention. The trial protocol was approved in the Iranian registry of clinical trials (identifier: IRCT20190325043111N1; <https://www.irct.ir/trial/43014>). This study was conducted as the M.D, thesis of Negar Botlani at the rheumatology department of this university.

Statistical analysis

In order to minimize bias, all densitometry was performed

and reported by a skilled technician. After collecting the study data, it was entered into SPSS-24 software. Descriptive data were reported as mean and percentage. Statistical tests of paired *t* test, *t* test, chi-square, Mann-Whitney U, Fisher's exact test and analysis of variance were used. $P < 0.05$ was considered as the significant level.

Results

In the present study, 190 postmenopausal women were evaluated, of which 180 were eligible for the study and were treated in two groups of 90 individuals with weekly doses of 35 versus 70 mg alendronate. Among the participants in the treatment group with a dose of 35 mg, 9 people (5 people due to non-adherence to treatment, 3 people due to lack of follow-up densitometry and one person due to death) and 19 people from the treatment group with a dose of 70 mg (4 individuals due to severe gastrointestinal problems, 8 due to lack of follow-up densitometry, 5 due to non-adherence to treatment, and 2 due to death) were excluded from the study (Figure 1).

A total of 152 postmenopausal women were randomly assigned to two treated groups at a weekly dose of 35 mg/alendronate (81 cases) and 70 mg/alendronate (71 cases). Demographic information of the two study groups was not statistically significant in terms of age, height, weight, BMI, menopause, disease or use of osteopenic predisposing drugs ($P > 0.05$). Table 1 shows the demographic information of the two groups.

The risk of fracture before the intervention showed that the probability of fracture of the femur and lumbar spine was significantly different in two groups.

After the intervention, we found no significant difference between the two groups in any of the fracture risk variables ($P > 0.05$). The results of the paired *t* test showed that the variables of fracture risk decreased significantly after the intervention ($P < 0.001$; Table 2).

The results on fracture risk score changes showed that the only probability of femoral fracture in the group

Table 1. Comparison of demographic variables in two groups with doses of 35 and 70 mg of alendronate

Variable	35 mg (n=81)	70 mg (n=71)	P value
Age	58.16±7.92	58.86±3.63	0.56
Height (cm)	158.00±5.91	156.63±6.76	0.18
Weight (kg)	69.91±9.50	67.97±10.15	0.22
BMI	28.14±4.53	27.86±4.41	0.70
Menopause (year)	9.62±7.021	9.01±5.38	0.56
Chronic disease			0.33
Pemphigus vulgaris	1 (2.8)	0 (0)	
Sjögren's syndrome	3 (8.3)	0 (0)	
Premature menopause	0 (0)	1 (3.3)	
Rheumatoid arthritis	26 (72.2)	25 (83.3)	
Systemic lupus erythematosus	6 (16.7)	4 (13.3)	
Taking medication			
Chronic corticosteroid use	30 (37.03)	23 (32.39)	0.62

Table 2. Comparison of mean fracture risk in two groups with 35 and 70 mg of alendronate before and after intervention

Variable	Dosage of the drug	Before intervention	After intervention	P value ^c
Probability fracture of femoral bone (%)	35	0.84	0.80	<0.001
	70	1.15	0.83	<0.001
P value		0.024 ^a	0.20 ^b	
Probability fracture of the vertebrae or wrist (%)	35	4.74	2.02	<0.001
	70	5.18	1.48	<0.001
P value		0.13 ^a	0.53 ^a	
Z-score spine	35	-0.20	0.84	<0.001
	70	-0.28	0.86	<0.001
P value		0.58 ^a	0.22 ^a	
Z-score hip	35	-0.23	0.84	<0.001
	70	-0.51	0.82	<0.001
P value		0.042 ^a	0.48 ^b	
T-score spine	35	-1.35	0.69	<0.001
	70	-1.57	0.60	<0.001
P value		0.035 ^a	0.74 ^b	
T-score hip	35	-1.29	0.72	<0.001
	70	-1.29	0.72	<0.001
P value		0.011 ^a	0.88 ^b	

^a t test; ^b Covariance analysis test; ^c Paired t test.

Table 3. Comparison of changes in mean fracture risk before and after intervention in two groups with 35 and 70 mg of alendronate

Variable	35 mg	70 mg	P value ^a
Probability fracture of femoral bone (%)	-0.35±0.34	-0.53±0.50	0.01
Probability fracture of the vertebrae or wrist (%)	-1.47±1.33	-1.76±1.19	0.15
Z-score spine	0.42±0.56	0.34±0.50	0.34
Z-score hip	0.38±0.52	0.48±0.52	0.23
T-score spine	0.43±0.46	0.43±0.36	0.97
T-score hip	0.52±0.60	0.56±0.52	0.71

^a t test.

treated with 70 mg/wk was significantly lower than in the 35 mg group ($P=0.01$; [Table 3](#)).

Discussion

Prevention of pathological fractures following osteoporosis is of great importance due to the therapeutic, psychological and costly burden on the health care system of each country. With the onset of aging in different societies, the incidence of osteoporosis is rapidly increasing in the community. Therefore, different societies seek to make decisions about treatment as well as the prevention of osteoporosis, however studies on the treatment of osteopenia have not yet reached a consensual conclusion (10, 13).

In the present study, two groups of postmenopausal women treated with weekly doses of 35 mg and 70 mg alendronate were evaluated over a 2-year treatment period. The two groups were not significantly different regarding demographic variables, underlying diseases, and the use of osteopenia-susceptible drugs. Additionally, the two groups were significantly different regarding densitometric findings, which due to the control of disruptive variables and the similarity of the two groups in terms of demographic variables, the results of analyzes can be attributed only to the effect of treatment. The results

of our study showed that treatment with both weekly doses of 35 or 70 mg of alendronate for two years resulted in a significant improvement in densitometric factors in the population of osteopenic women, while the overall comparison of the two therapeutic doses did not differ significantly.

While the latest guideline introduced in Japan recommends the preventive use of alendronate in osteopenic women under the above conditions (11), the study of Moriwaki et al, in a 5-year evaluation did not yield results in agreement with this guideline (14). Schousboe et al, also emphasized that preventive treatment with alendronate was not economically viable in terms of its preventive effect on hip fractures (10). In line with our study, Capiglioni et al evaluated treatment with alendronate in postmenopausal women for a period of one year and reported positive results regarding limiting bone resorption and increasing bone densitometric quality (15).

In comparing the two therapeutic doses, the two-year follow-up results of the two groups showed no significant difference in any of the densitometric factors. Given the cost of treatment and cost-effectiveness, a 35 mg/wk dose may be more cost-effective for prevention in osteopenic women. According to other studies, gastrointestinal

irritation and esophageal ulcers are the most common complaints of patients with bisphosphonates (16). One of the most important limitations of our study is the lack of evaluation of these two factors in following up on patients for two years. However, no significant difference in the two administered doses could be in favor of using a lower dose to prevent gastrointestinal complications.

In a one-year study, Li and colleagues evaluating two doses of 70 mg/wk and once every two weeks in the postmenopausal population with osteopenia and osteoporosis, both therapies resulted in significant improvements in densitometric improvements, since similar to our study, no significant differences were found between the two treatments (16).

In another study, Schnitzer et al evaluated the effect of alendronate daily at a dose of 10 mg compared to a dose of 70 mg/wk. They reported significant gastrointestinal side effects and esophageal ulcers that were higher in daily doses, while the results of improvements in bone densitometric findings were found similar in two groups. Therefore, they recommended a weekly dose (17).

The findings of the above two studies are in line with the present study. Given the long-term effectiveness of alendronate and similar effects at different doses, it can be argued that lower weekly doses should be used to prevent possible gastrointestinal side effects as well as cost-effectiveness.

Previously, Shiraki and colleagues compared doses of 2.5 mg/d and 10 mg/d of alendronate for the treatment of osteoporosis. They showed, the effectiveness of alendronate depended on the administered doses and the results were significantly better with higher doses (18). The interesting point in their study, which is completely different from other studies, is the statistically significant difference between the dose of 2.5 mg and 10 mg. This may be due to the low-dose effect of 2.5 mg/d compared to 10 mg/d. On the other hand, in their study, gastrointestinal side effects have not been studied while; it is one of the points that can be effective in deciding on the prescribed dose.

Choi et al, also administered a 20 mg/wk dose for 12 weeks of treatment with alendronate and showed that this weekly dose could improve the densitometric status of postmenopausal women (19). One of the highlights of this study is the positive result obtained with a low-weekly dose of 20 mg. However, the decision on the dose and timing of alendronate administration still needs further evaluation.

Conclusion

According to our research, this study for the first time in Iran evaluated the effect of preventive treatment and dose adjustment of alendronate in postmenopausal women. The results of our study reported favorable results in the preventive treatment of alendronate in osteopenic women. Due to the lack of statistically significant differences in

high-dose versus low-dose treatment, it seems more cost-effective to use a weekly dose of 35 mg. In addition, due to gastrointestinal irritation, which is the main complaint of alendronate use, a weekly dose of 35 mg was found with similar results compared to a dose of 70 mg.

Limitations of the study

The most important limitation of our study is the lack of review and comparison of the side effects of alendronate use, as this is associated with side effects such as gastrointestinal irritation.

Authors' contribution

MK and AS were the principal investigators of the study. NB was included in preparing the concept and design, and revised the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interests

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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