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Original

# Effect and safety of alendronate on bone density in patients with chronic kidney disease; a controlled double blind randomized clinical trial

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## Abstract

**Introduction:** With decline of glomerular filtration rate (GFR), a number of metabolic bone diseases such as osteoporosis are simultaneously caused. We evaluated the results of alendronate on bone density in patients with chronic kidney disease (CKD).

**Objectives:** The main aim of the study was evaluation of the changes in bone density, one year after treatment by dual energy x-ray absorptiometry technique.

**Patients and Methods:** We evaluated two treatment regimens on bone density of 44 patients between 18-45 years old (22 in experimental and 22 in control group) in a controlled double blind randomized trial. The experimental group was prescribed alendronate (10 mg), calcitriol (0.25 μg) and calcium carbonate (1500 mg) daily. The control group was treated with the same regimen except for alendronate.

**Results:** After completion of the trial, bone density decreased in all patients in the control group, but increased in the experimental group, in lumbar spine and femoral neck, 6.4% and 4.5% respectively. Alendronate was well tolerated.

**Conclusion:** Alendronate is safe in these patients and increases the bone density in CKD stage 1 and 2.

Keywords: Alendronate; Bone density; Chronic kidney disease

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## Introduction

Osteoporosis is described by a diminution in bone mass which is more common in women during menopause. However it can also occur in men and women who have major demineralization risk factors and underling diseases. Usually, the clinical presentation of osteoporosis is the fracture of the hip and spine, although fractures can occur in any part of the body (1). According to the World Health Organization (WHO), osteoporosis and osteopenia are defined as a decrease of bone mass by at least 2.5 and one standard deviation (SD) lower than mean in comparison with young healthy people, respectively (2). Chronic kidney disease (CKD) is one of the diseases which is related to osteoporosis and metabolic bone disease. The relationship between bone disease and CKD was discovered more than 60 years ago. Causes of metabolic bone disease in CKD include secondary hyperparathyroidism, metabolic acidosis, and osteomalacia, treatment with corticosteroid, cytokines and growth factors (3). The treatment of osteoporosis in CKD patients consists of treatment of osteoporotic fractures, specifically underling disease, calcium and vitamin D deficiencies (4).

## Objectives

Recently, the use of bisphosphonates has been advocated in CKD treatment. Therefore we decided to evaluate the effect of bisphosphonate on bone mass density in CKD patients.

## Patients and methods

### *Study patients*

This study is a controlled double blind randomized clinical trial. Forty-four CKD patients between 18 to 45 years old were enrolled in the study. Participants were assigned randomly to either intervention or control group with 22 patients in each group with resembling age and gender

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**Implication for health policy/practice/research/ medical education**

In a study on 44 chronic kidney disease (CKD) patients, we found that alendronate is a safe and effective agent for treatment of osteoporosis in CKD of stages I and II.

characteristics. Randomization was done by computer.

### *Inclusion criteria*

All of them were in CKD stage I and II according to glomerular filtration rate (GFR) (estimated using the Cockcroft-Gault formula) and had bone density at least one SD lower than normal level for the same age and gender.

### *Exclusion criteria*

Patients with diabetes mellitus, cirrhosis, peptic ulcer disease, advanced CKD, hyperparathyroidism, Paget disease and patients who had history of pervious treatment with bisphosphonate, estrogen and steroid were excluded (5).

### *Intervention*

The intervention group received 10mg alendronate, 25 µg calcitriol and 1500mg calcium carbonate daily for one year. The control group received the same regimen except for alendronate.

### *Laboratory and paraclinical assessments*

Calcium, phosphorus and alkaline phosphatase was checked before beginning and every 2 months until completion of the study by standard kits. Parathyroid hormone was checked at the beginning and the end of the study by ELISA method.

Densitometry was done by dual energy x-ray absorptiometry, at the beginning of the trial and reevaluated again one year later by the same instrument and the same technicians.

The primary end point was bone mineral density (BMD) changes in femoral neck and lumbar vertebrae in one year.

### *Ethical issues*

The research followed the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Ahvaz Jundishapour University of Medical Sciences. All of the patients provided written informed consent.

### *Statistical analysis*

Data are represented as mean values ± SD. For comparison between the control and interventional group, student *t* test was used. For comparison of the data in a group, paired *t* test was used. Fisher exact test was used to compare the side effects between two groups. The *P* value was calculated between the interventional and control group by student *t* test. A *P* value <0.05 was considered statistically significant. All data were analyzed with SPSS version 21.

## Results

Participants were randomly assigned to either intervention or control groups with 22 patients in each group, with resembling age and gender characteristics. Forty-five percent of intervention and 50% of control group were women. All of the women were premenopausal.

The mean age in women and men was 39 ± 7 years and 44 ± 10 years, respectively ($P > 0.1$). The mean body mass index (BMI) in intervention group and control group was 24 ± 5 kg/m$^2$ and 23 ± 7 kg/m$^2$, respectively ($P > 0.1$; Table 1).

The mean blood urea nitrogen (BUN) and creatinine had no significant difference between the two groups. BUN in the intervention and control group was 31 ± 9 mg/dl and 32±7 mg/dl, respectively ($P > 0.1$).

Serum creatinine (Cr) in intervention and control group was 1.8±0.32 mg/dl and 2 ± 0.91 mg/dl, respectively, which had no statistical difference ($P > 0.1$).

Upon completion of the study, BUN and Cr were measured and compared again in both groups which did not show a significantly statistical difference ($P > 0.5$).

Parathyroid hormone (PTH) was measured in both groups prior to the study which did not have statistically significant difference ($P > 0.1$).

Upon completion of the study, PTH was measured again in both groups, which showed a statistically significant difference in comparison with basal PTH. The results of parathyroid hormone assessment before and after intervention were 343 ± 241 pg/ml and 152 ± 85 pg/ml in the alendronate group, respectively and 346 ± 180 pg/ml and 187 ± 117 pg/ml in the control group, respectively ($P < 0.001$; Table 2).

In the intervention group, the mean bone density according to T-Score was -1.69 ± 1 g/cm$^2$ in L2-L4 region (maximum -0.4 g/cm$^2$ and minimum -3.5 g/cm$^2$). Prevalence of osteopenia and osteoporosis in the lumbar spine in the intervention group were 26% and 67%, respectively.

**Table 1.** Demographic information of the patients

| Parameter | Case | Control | *P* value |
|---|---|---|---|
| F/M | 10/12 | 11/11 | > 0.1 |
| Perimenopause | 10 | 11 | > 0.1 |
| Menopause | 0 | 0 | > 0.1 |
| Female age (y) | 39±7 | 40±6.7 | > 0.1 |
| Male age (y) | 44±10 | 40.11 | > 0.1 |
| BMI (kg/m$^2$) | 24±5.2 | 23±7 | > 0.1 |

Abbreviations: BMI, body mass index; F, female; M, male.

**Table 2.** Biochemical data and side effect of the patients

| Parameter | Case | Control | *P* value |
|---|---|---|---|
| GI problem | 0 | 0 | > 0.1 |
| Ca1 (mg/dl) | 9.3 | 9.2 | > 0.1 |
| Ca2 (mg/dl) | 9.7 | 9.8 | > 0.1 |
| ALP (Iu/dl) | 213±119 | 200±111 | > 0.1 |
| PTH1 (pg/dl) | 343±214 | 346±180 | > 0.1 |
| PTH2 (pg/dl) | 152±86 | 187±115 | > 0.1 |
| BUN1 (mg/dl) | 33±9.2 | 33±7.7 | > 0.1 |
| BUN2 (mg/dl) | 33±7.7 | 34±10 | > 0.1 |
| Cr1 (mg/dl) | 1.8±0.32 | 2±0.91 | > 0.1 |
| Cr2 (mg/dl) | 1.8±0.34 | 2.2±1 | > 0.1 |

Abbreviations: GI, gastrointestinal; Ca, calcium, ALP, alkalinphosphatase; BUN, blood urea nitrogen; Cr, creatinine; PTH, parathyroid hormone.

The mean bone density of femoral neck in this group was -2.38 ± 0.86 g/cm², (minimum -4 g/cm² and maximum -0.7 g/cm²).

Prevalence of osteopenia and osteoporosis of femoral neck were 6.6% and 93.4%, respectively. In the control group, the same mentioned ratios were nearly established.

After one year of treatment with alendronate, the second BMD was measured and results were calculated according to percent in comparison with mean basal BMD in each group.

In the second BMD, improvement in mean bone mass density, in lumbar spine (L2-L4) in intervention and control group were 6.4 ± 5.9% and 3.42 ± 0.44%, respectively ($P < 0.001$).

In the femoral neck, improvement in mean bone density in alendronate group and control group were 4.5 ± 5% and 3.7 ± 0.1%, respectively ($P < 0.001$). Table 3 shows the improvement in mean BMD in lumbar was more than femoral neck in case group.

## Discussion

We found that alendronate increases BMD in mild to moderate CKD. It seems to be more effective in lumbar spine than femoral neck.

In a study by Jamal et al, the effect of alendronate on lumbar was also higher than total hip. This mentioned trial was performed on women with a range of GFR from normal to reduced, in comparison to our study in which the participants were men and women, and GFR was reduced in all of them. They found reasonable evidence for efficacy of alendronate, and concluded that the patients should be treated to prevent crippling fractures. They also found increasing spine BMD and decreasing spine and non-spine fractures in women with and without reduced GFR, contrary to the impression increasing in total hip BMD with alendronate, slightly greater among women with reduced GFR (5). In comparison to our study, all of the patients in their trial were women and patients with normal GFR were enrolled, which might have influenced the efficacy of intervention. In previous studies the reported overall rate of increase in bone mass was 3%-7% (6). In transplant patients, treatment with etidronate, increases BMD, 4.3% and 10% in lumbar spine and femoral neck, respectively. Similarly, treatment with alendronate in transplant patients, increases bone mass density, 3.4% and 1.6%, respectively (7).

A study by Omidvar et al compared the effect of alendronate and pamidronate on bone loss in renal transplant patients for the first 6 months after transplantation. They concluded that pamidronate seems to be comparable to alendronate in attenuating early bone loss in kidney transplant patients, as significantly less reduction of BMD was seen in the femoral neck and femur in the pamidronate group (8). In our trial, alendronate was more effective in lumbar spine than femoral neck. In that trial alendronate was well tolerated and mild dyspepsia was only observed in 3 patients (8).

In our study, gastrointestinal complications were similar in both the control and intervention group sand no patient was forced to discontinue the drug.

In a study by Shahbazian et al, the efficacy and safety of alendronate in the prevention of bone loss in renal transplant recipients was evaluated. They found that the BMD in patients treated with alendronate increased significantly both at the lumbar vertebrae and femoral neck while it decreased in the placebo group. Alendronate was safe and tolerated well in that trial similar to our study (9).

We expected the PTH level to rise, but it did not. Physiologically, because of anti-osteolytic effect of alendronate, secondary hyperparathyroidism exacerbates in CKD (10). This may suggest that the efficacy of therapeutic regimen consists of calcium and vitamin D in both groups. However, this did occur in this trial which may be related to better control of hyperphosphatemia and treatment of vitamin D deficiency in both groups.

At the end of the study, parathyroid hormone had reached therapeutic range in both groups.

Bone density was distinctly lower in patients with low BMI, but response to treatment was similar to others.

In the present study, prevalence of osteoporosis in lumbar spine and femoral neck was 67% and 93.4% respectively which increased after treatment explanatory for significant statistical changing and suggested that response to treatment in intervention group. In a study by Reyes et al,

**Table 3.** BMD data of the patients

| Parameter | Case | Control | *P* value |
|---|---|---|---|
| Prevalence of osteopenia (L2-L4) (%) | 26 | 29 | > 0.1 |
| Prevalence of osteoporosis (L2-L4) (%) | 67 | 71 | > 0.1 |
| Lower BMD (L2-L4) (g/cm²) | -3.5 | -3.5 | > 0.1 |
| Higher BMD (L2-L4) (g/cm²) | -0.4 | -0.3 | > 0.1 |
| Prevalence of osteopenia (femoral neck) (%) | 6.6 | 10 | > 0.1 |
| Prevalence of osteoporosis (femoral neck) (%) | 93.4 | 90 | > 0.1 |
| Lower BMD (femoral neck) (g/cm²) | -4 | -3.8 | > 0.1 |
| Higher BMD (femoral neck) (g/cm²) | -0.7 | -0.7 | > 0.1 |
| Mean BMD (L2-L4) (g/cm²) | -1.69±1 | -1.4±1.1 | > 0.1 |
| Mean BMD (femoral neck) (g/cm²) | -2.38±0.86 | -1.9±1.02 | > 0.1 |
| BMD improvement (L2-L4) (%) | 6.4±5.9 | 3.42±0.44 | 0.001 |
| BMD improvement (femoralneck) (%) | 4.5±5 | 3.7±0.1 | 0.001 |

Values represent as mean±SD. The P value is calculated between the intervention and control group by *t* test.
Abbreviations: BMI, body mass index; BMD, bone mass density.

the overall rate of osteoporosis was reported to be 55%-87% (11). The prevalence of osteoporosis in our patients was much higher which may be related to secondary hyperparathyroidism that was also higher in our patients.

As the safety and efficiency of bisphosphonates may be different in patients with CKD, the effects on vascular calcifications need further study, because low bone turn over may exacerbate vascular calcifications in these patients (12).

Although many studies have been done on the effect of bisphosphonates on BMD in patients with mild CKD, several questions about the safety and efficacy of bisphosphonates in patients with more advanced kidney disease remain unanswered.

## Conclusion

We concluded that alendronate is a safe and effective agent for treatment of osteoporosis in CKD stage I and II. In this regard, a cohort study for decreasing risk of fracture is recommended in these patients.

## Limitations of the study

The major limitation of our study was the relatively small number of patients. Also, safety and efficacy of alendronate can be evaluated in moderate and advanced stages of CKD with more patients.

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## Authors' contribution

HSH and SKM designed the research. MSH conducted the research. FH analyzed the data, LY, MRT and SHSH prepared the primary draft. HSH, SKM, SHSH, FH, MRT, LY and MSH critically reviewed and gave the final approval. All authors contributed equally to data acquisition.

## Conflicts of interest

The authors declared no competing interests.

## Ethical considerations

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

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