



# Assessment the efficacy and safety of denosumab use for treatment of osteoporosis in hemodialysis patients

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## Abstract

**Introduction:** Osteoporosis is common in patients with chronic kidney disease (CKD) that could direct to metabolic abnormalities and accelerate bone loss. The administration of bisphosphonates for the management of osteoporosis is contraindicated in cases with severe kidney impairment.

**Objectives:** In the current investigation, we assess the effectiveness and safety of denosumab administration for the therapy of osteoporosis in hemodialysis (HD) individuals.

**Patients and Methods:** Seventy-four HD cases with osteoporosis who were received denosumab were assessed retrospectively. All individuals received supplemental vitamin D. Serum calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase (ALP) had been measured every three months. Denosumab efficacy was measured by assessing the alterations of bone mineral density (BMD) and plasma ALP.

**Results:** The mean values of T-score of the spine and hips in HD patients after treatment with denosumab when compared with before treatment was not statistically significant ( $P=0.7019$  and  $P=0.494$  respectively). There was a low mean serum ALP in the HD patients after treatment with denosumab when compared with before treatment, but not statistically significant ( $P=0.0625$ ). Plasma calcium concentration decreased shortly after the injection of denosumab however returned within fourteen days. Supplementary vitamin D (1.0 to 1.5  $\mu\text{g/day}$ ) looked to prevent hypocalcemia and support long treatment with denosumab.

**Conclusion:** Our study suggests that denosumab is not associated with increases in the BMD of the spine and hip in patients with CKD on HD and hypocalcemia is a concern complication.

**Keywords:** Bisphosphonates, Denosumab, Osteoporosis, Hemodialysis

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## Introduction

Chronic kidney disease (CKD) is a major and important risk factor for osteoporosis (1-4). Increased risk for osteoporosis in patients with CKD may be due to several reasons, such as advanced age and female gender, hyperparathyroidism, hypogonadism, abnormalities of vitamin D metabolism and chronic metabolic acidosis accelerate bone loss (5). Likewise, glucocorticoids used for the treatment of glomerulonephritis can induce osteoporosis (6).

For the treatment of osteoporosis, bisphosphonates are the most common drugs used. They decrease the risk of fracture in the short term, but there is no proof for its effectiveness in long-term treatment (7,8). However, bisphosphonates may result to the worsening of renal function and are not suggested, for administration in

cases with serious renal disturbance (9,10).

The formation, activation, and survival of osteoclasts depend on the receptor activator of the nuclear factor-kappa B ligand (RANKL) (11). Denosumab binds RANKL with high affinity and specificity, inhibiting activation of its cognate receptor RANK, which is upregulated on the surface of osteoclasts and osteoclast precursors. Consequently denosumab (as a human monoclonal antibody for osteoporosis treatment) inhibits osteoclast maturation, activation, and survival, hence decreasing resorption of bone and improving the structural strength of bone (12,13). Numerous studies showed a persistent reduction of bone turnover, and bone mineral density (BMD) increased with a low incidence of fracture (12,14,15).

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### ■ Implication for health policy/practice/research/medical education

Seventy-four hemodialysis (HD) cases with osteoporosis who were administered with denosumab (as a human monoclonal antibody for osteoporosis treatment) were analyzed retrospectively. Serum calcium, alkaline phosphatase (ALP), phosphate and parathyroid hormone (PTH), were assessed every three months. Denosumab efficacy was evaluated by analyzing the alterations in bone mineral density (BMD) and plasma ALP. There was no statistically significant difference in the mean values of T-score of the spine and hip in HD patients after treatment with denosumab when compared with before treatment. There was also a low- mean serum ALP in the HD patients after treatment with denosumab when compared with before treatment, but not statistically significant. Our study suggests that denosumab is not associated with increasing the BMD of the spine and hip in cases with chronic renal failure on HD since hypocalcemia is a concern complication too.

### Objectives

There are rare data and it is indefinite whether denosumab administration for osteoporosis is effective and safe in case with chronic renal failure, particularly hemodialysis (HD) patients. In this investigation, we assessed the effectiveness and adverse effects of denosumab use for osteoporosis therapy in HD cases.

### Patients and Methods

#### Study design

A total of 74 patients with end-stage kidney disease (ESKD) on conventional HD, three sessions per week of more than six months duration at Al-Khezam dialysis center, Al Adan hospital, and Farwanya hospital dialysis center, Kuwait, who had been treated with denosumab for osteoporosis were examined retrospectively. All studied patients received vitamin D (1.0 to 1.5 µg/day) and underwent a complete history and regular physical examinations.

Blood chemistry including kidney function tests and CBC measurements was done. Serum calcium, phosphate, intact parathyroid hormone (iPTH), and alkaline phosphatase (ALP) had been measured every three months. As serum ALP is released from bone-resorbing osteoclasts, hence it is conducted as an indicator for bone resorption (16). BMD measurement every six months before and after denosumab treatment.

#### BMD measurement

Dual-energy X-ray absorptiometry (DEXA) was directed for measuring BMD at the spine and femur neck before starting of denosumab and each six months subsequently. Classification of BMD values was conducted according to WHO criteria; a T-score of -1.0 and above is considered normal, a T-score between -1 and -2.5 reflects osteopenia, and a T-score of -2.5 and below reflects osteoporosis (17).

#### Statistical analysis

Paired *t* tests were employed to compare T-score values

recorded at baseline with those recorded after every six months of treatment with denosumab. Spearman's rho was used to assess the correlation coefficient between T-score and duration of denosumab treatment and between serum ALP and duration of denosumab treatment. A *P* value of 0.05 was conducted as a statistically significant level. All statistical analysis were performed using MedCalc software (version 5, 2019 MedCalc Software, San Diego, CA, USA.).

### Results

The demographic and clinical characteristics of patients are demonstrated in Table 1. A total of 74 HD individuals with osteoporosis were included in this investigation. All patients had received denosumab as the first therapy for osteoporosis. The mean age of the patients was 59.15± 16.1 years; the mean dialysis duration was 65.6±36.8 months, while the mean denosumab treatment duration was 19.135±16.218 months. The main causes of ESKD were diabetes mellitus, hypertension), glomerulonephritis, chronic tubule-interstitial nephritis, and adult polycystic kidney disease.

The laboratory parameters of the HD patients included in the study before and after denosumab use are shown in Table 2. There was a statistically significant low mean value of serum calcium in HD patients after treatment with denosumab when compared with before treatment (2.31±0.139 versus 1.92±0.25 respectively, *P*=0.0001; Table 2). There was a statistically significant high mean value of 25-OH vitamin D3 in HD patients after

**Table 1.** Demographic and clinical characteristics of the studied hemodialysis patients

| Variables                             |               |
|---------------------------------------|---------------|
| Age (y)                               | 59.15± 16.1   |
| Gender (M/F)                          | 13/61         |
| Duration of denosumab treatment (mon) | 19.135±16.218 |
| Number of doses                       | 3.24± 2.72    |
| Duration of dialysis (mon )           | 65.6±36.8     |
| BMI (kg/m <sup>2</sup> )              | 25.3±3.8      |
| SBP (mm Hg)                           | 151.7±17.8    |
| DBP (mm Hg)                           | 95.8±11.8     |
| Mean BP (mm Hg)                       | 114.4±13.9    |
| Etiology of ESKD                      |               |
| Diabetes mellitus                     | 51(68.9%)     |
| Hypertension                          | 9 (12.2%)     |
| Lupus nephritis                       | 3 (4.1%)      |
| Glomerulonephritis                    | 3 (4.1%)      |
| APKD                                  | 2 (2.7%)      |
| CH TIN                                | 1 (1.35%)     |
| Dysplastic                            | 1 (1.35%)     |
| HUS                                   | 1 (1.35%)     |
| Unknown                               | 2 (2.7%)      |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; ESKD, End-stage kidney disease; APKD, adult polycystic kidney disease; CH TIN, chronic tubule-interstitial nephritis; HUS, hemolytic uremic syndrome.

**Table 2.** Laboratory parameters of the studied HD patients

|                    | Before denosumab treatment  | After denosumab treatment | P value |
|--------------------|-----------------------------|---------------------------|---------|
| Serum calcium      | 2.31± 0.139                 | 1.92± 0.25                | 0.0001  |
| Serum PO4          | 1.54± 0.63                  | 1.37± 0.59                | 0.0923  |
| Serum iPTH         | 90.32± 117.94               | 128.75± 110.17            | 0.0423  |
| Serum 25-OH Vit D  | 44.79± 32.67                | 62.28± 38.19              | 0.0032  |
| Serum ALP          | 132.76± 97.195              | 107.917±59.267            | 0.0625  |
| T-score (spine) SD | -2.5205±1.1498<br>M -2.7000 | -2.389±1.0414<br>M-2.4000 | 0.7019  |
| T-score (hip) SD   | -2.8528±0.7394<br>M-2.9000  | -2.889±1.2242<br>M-3.3000 | 0.4936  |

PO4, phosphorus; iPTH, intact parathyroid hormone; 25-OH Vit D, 25-hydroxy vitamin D; ALP, alkaline phosphatase; SD, standard deviation.

**Table 3.** Variations in serum calcium after denosumab treatment

| Variable               | Before denosumab use | Two days after denosumab use | 14 days after denosumab use | P-value |
|------------------------|----------------------|------------------------------|-----------------------------|---------|
| Serum calcium (mmol/L) | 2.31± 0.139          | 1.61±0.23                    | 1.82± 0.24                  | 0.0001  |

treatment with denosumab when compared with before treatment (44.79±32.67 versus 62.28±38.19 respectively,  $P=0.0032$ ; Table 2). There was a statistically significant high mean value of iPTH in HD patients after treatment with denosumab when compared with before treatment (90.32±117.94 versus 128.75±110.17 respectively,  $P=0.0423$ ; Table 2).

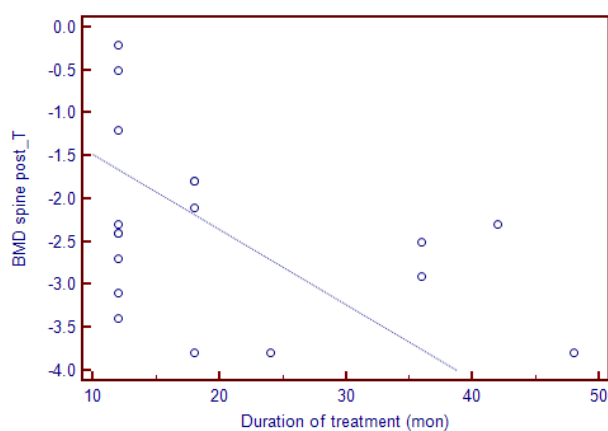
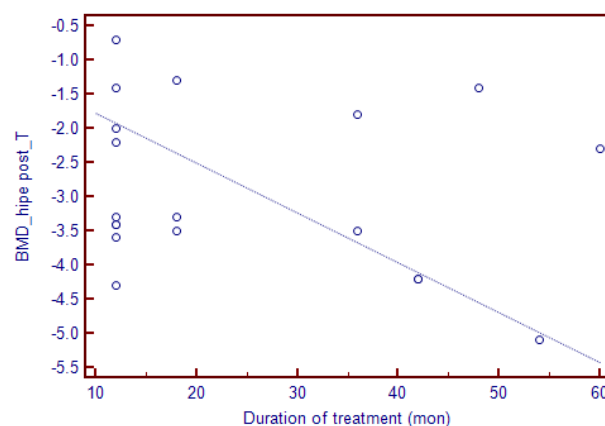
There was no statistically significant difference in the mean values of T-score of the spine in HD patients after treatment with denosumab when compared with before treatment (-2.5205±1.1498 versus -2.389±1.0414,  $P=0.7019$ ) and there was no statistically significant difference in the mean values of T-score of the hip in the HD patients after treatment with denosumab when compared with before treatment (-2.853±0.739 versus -2.889±1.224,  $P=0.494$ ) and low mean serum ALP in the HD patients after treatment with denosumab when compared with before treatment, but not statistically significant (132.76±97.195 versus 107.917±59.267,

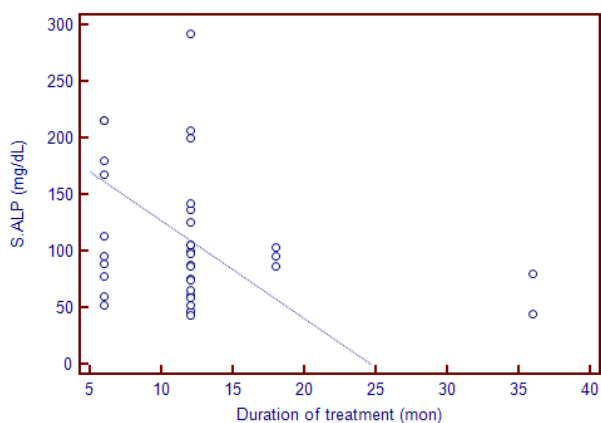
$P=0.0625$ ; Table 2).

Using Spearman's correlation coefficient analysis, no statistically significant negative correlations between T-score values of the spine after treatment with denosumab and duration of denosumab treatment was detected ( $r= -0.344$ , 95% CI -0.699 to 0.146 for  $r$ ,  $P=0.1620$ ; Figure 1). Additionally, no statistically significant negative correlations between T-score values of hip after treatment with denosumab and duration of denosumab treatment ( $r=-0.195$ , 95% CI -0.597 to 0.284 for  $r$ ,  $P=0.4230$ ; Figure 2) was seen. There was no statistically noteworthy negative association between serum ALP value after treatment with denosumab and duration of denosumab treatment ( $r=-0.238$ , 95% CI -0.526 to 0.0980 for  $r$ ,  $P=0.1618$ ; Figure 3).

#### Variations in serum calcium after denosumab administration

After denosumab administration in HD patients, plasma

**Figure 1.** Correlation coefficient between bone mineral density (BMD) of the spine and duration of denosumab treatment ( $r= -0.344$ , 95% CI -0.699 to 0.146 for  $r$ ,  $P=0.1620$ )**Figure 2.** Correlation coefficient between bone mineral density in the hip and duration of denosumab treatment ( $r=-0.195$ , 95% CI -0.597 to 0.284 for  $r$ ,  $P=0.4230$ ).



**Figure 3.** Correlation coefficient between ALP and duration of denosumab treatment ( $r=-0.238$ , 95% CI -0.526 to 0.0980 for  $r$ ,  $P=0.1618$ ).

calcium was determined every two days. Shortly after denosumab therapy, serum calcium started to decline. The reduction of plasma calcium is differed according to the dose of vitamin D supplementation. A vitamin D amount of 1.0 to 1.5  $\mu\text{g}/\text{day}$  was connected with the preservation of plasma calcium concentration. Even though plasma calcium decreased shortly after denosumab use, its levels in all patients recovered after 14 days (Table 3).

## Discussion

The present study demonstrated that mean values of T-score of the spine and femur neck were not increased in HD patients after treatment with denosumab when compared with before treatment and that serum ALP decreased in HD patients after treatment with denosumab when compared with before treatment but not statistically significant.

Osteoporosis is common in patients with CKD with progressive bone loss, and increased incidence of bone fractures. Various factors may possibly clarify the relationship amongst CKD and osteopenia or osteoporosis such as old age and lower concentration of vitamin D. Moreover, there is increasing evidence that CKD itself is a risk factor for low-BMD (1-3). Individuals with CKD was detected to have more rates of bone loss (3). There is an independent association amongst an estimated glomerular filtration rate below 60 mL/min/1.73 m<sup>2</sup> and the prevalence of hip fractures (18). Furthermore, increased serum cystatin C levels in patients with CKD have been independently associated with risk for hip fracture (19).

For the treatment of osteoporosis, bisphosphonates are commonly used. However, several studies revealed that bisphosphonates are not efficient for longstanding improvement in BMD (7,8). Moreover, many studies showed poor medication adherence with bisphosphonates (20).

Compared with bisphosphonates, denosumab is a potent antiresorptive with anti-fracture efficacy. Denosumab

inhibits osteoclast maturation, activation, and survival, therefore lessening resorption of cortical and trabecular bone, whereas bisphosphonates affect mature osteoclasts (12). This evidence can illuminate why denosumab seems to be more applicable than bisphosphonates as a therapy for low-BMD.

Unfortunately, our study revealed that treatment with denosumab for a mean of  $19.135 \pm 16.218$  months duration in HD patients with osteoporosis was not associated with an increase in the BMD of the spine, and hope that serum ALP levels decreased in HD patients after treatment with denosumab but was no statistically significant difference when compared with before treatment. Our results regarding BMD are not in agreement with many previous studies as Hiramatsu et al (21) and Suzuki et al (22) revealed that denosumab is an applicable treatment for osteoporosis in patients with CKD. The explanation of our negative results regarding the efficacy of denosumab treatment for osteoporosis is that all our studied patients were on HD and regular HD may affect the pharmacokinetics and pharmacodynamics of denosumab. In addition, our study included a small sample of patients and a short duration of denosumab treatment.

In addition, our study evaluates the adverse effects of denosumab treatment in HD cases. Hypocalcemia was a common adverse effect shortly after denosumab use in HD patients. Our findings indicate that vitamin D supplementation is necessary to prevent hypocalcemia and preferably should be began before treatment with denosumab. Higher doses of vitamin D supplementation are necessary before the treatment of denosumab for individuals on HD. However, values of plasma calcium recovered in fourteen days in cases. A dose of 1.0 to 1.5  $\mu\text{g}/\text{day}$  of vitamin D was required to keep serum calcium during treatment with denosumab and monitoring of serum calcium is important. Our results regarding the adverse effect of denosumab treatment are in agreement with the study of Hiramatsu et al (21), Suzuki et al (22), and Ullah et al (23) who revealed hypocalcemia was a common complication of denosumab treatment particularly in HD patients. the administration of denosumab in patients with high bone turnover creates a situation similar to "hungry bone syndrome (24) leading to a sudden influx of calcium into the bone necessary for bone mineralization and remodeling. Severe hyperparathyroidism aggravated by low-vitamin D status may be responsible for severe hypocalcemia in our patients following denosumab therapy. Conversely, denosumab-induced hypocalcemia in dialysis patients can occur in the absence of inappropriate high PTH, which could be due to concomitant vitamin D deficiency (25).

## Conclusion

Our study suggests that denosumab is not associated with increases in the BMD of the spine and hip in patients with CKD on HD and hypocalcemia is a concern complication.

The reduction in serum calcium levels following the treatment of denosumab provides evidence for the significance of sufficient vitamin D supplementation during treatment. Further studies with a big sample of HD patients and a long duration of denosumab treatment are needed.

### Limitations of the study

There are some limitations in our study such as the small number of patients included in this study and the study done in two dialysis centers only in Kuwait. Further studies with a big sample of HD patients, more dialysis centers, and a long duration of denosumab treatment are needed.

### Authors' contribution

EA was the principal investigator of the study and project administration. EA, BA, RA and AA were included in conceptualization, methodology, validation, formal analysis, investigation, resources and data curation. EA, MK, GN, AR, MM, YE, EA, AE, MH, MA, SA, MK, AS, SA, AA and NA wrote, reviewed and edited the manuscript. All authors participated in writing-original and final draft of the manuscript, visualization and supervision of the manuscript. All authors have read and approved the contents of the manuscript and confirmed the accuracy and the integrity of any part of the work.

### Conflicts of interest

The authors declared that they have no conflict of interest.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. The Ethics Committee of Kuwait Institute for Medical Specializations (KIMS) approved this study protocol. Accordingly written informed consent was taken from all participants before any intervention. Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

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