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ORIGINAL ARTICLE

Effect of denosumab treatment on bone mineral density and bone turnover markers in osteoporotic patients: real-life experience 2-year follow-up

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Abstract

Summary Denosumab leads to improvements in BMD levels and is a well-tolerated agent according to results of randomized controlled studies but results in real-life setting are important to evaluate drug adherence and real-life efficiency. In this study, we present the results of 305 patients that were treated with denosumab in our clinic.

Introduction The long-term efficacy of anti-osteoclastic drugs in treatment of osteoporosis is well known. Denosumab, a novel human monoclonal antibody, is an anti-osteoclastic agent that has been shown to lead to reductions in vertebral, nonvertebral, and hip fracture risk in randomized and observational studies. Real-life data of this agent is increasing. In this study, we presented our real-life data about the 2-year follow-up of patients under denosumab treatment.

Methods Osteoporotic patients who were treated with at least one denosumab injection between 2014 and 2020 years were included. Clinical and demographic data, bone turnover markers, and radiological reports (bone mineral densitometry (BMD), vertebral x-ray) were obtained from patient files retrospectively.

Results A total of 305 patients (f/m: 275/30, 68.1 ± 11.05 years) were included. The median injection number was 4 (1–10). Two hundred seventy-three patients (89.8%) were persistent on treatment at the 12th month; 175 patients (57.3%) were persistent at 24th month. Sixty-eight patients (22%) were not using denosumab anymore, 55 of the patients were not continuing by doctor desicion and 13 were not continuing due to patient-related causes. Median BMD levels significantly increased from 0.809 (0.2–1.601, IQR: 0.136) to 0.861 (0.517–1.607, IQR: 0.14) in L1–L4 and from 0.702 (0.349–0.997, IQR: 0.125) to 0.745 (0.508–1.008, IQR: 0.137) in femur area at the 24th month of treatment. An improvement of 8.04% in L1–L4 BMD and 4.5% in femur neck BMD levels at the 24th month of treatment was observed. There was a significant decrease in bone turnover markers at the 24th month of treatment.

Conclusion In our group of patients under denosumab treatment, 53% of persistence was found at 24 months and associated with improvement in BMD levels without any significant side effects except one case with urticarial reaction. Denosumab leads to improvements in BMD levels and is a well-tolerated agent in a real-life setting comparable to results of randomized controlled studies in patients with different comorbidities.

Keywords Denosumab · Bone mineral density · Real-life experience

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Introduction

Osteoporotic fractures are a major health concern worldwide and are associated with functional limitation, increased morbidity, and mortality [1–3]. As the fracture risk increases with advancing age and the population is aging worldwide, the burden of osteoporosis will continue to grow.

Although numerous medications are approved for osteoporosis treatment, many patients are not being treated, and drug adherence is also poor [4, 5]. In postmenopausal women, medicines that decrease osteoclastic bone resorption like estrogen and bisphosphonates are known to prevent bone loss and reduce the risk of fracture [6, 7]. But, limitations of oral bisphosphonates due to gastrointestinal tract irritation, poor medication adherence, and chronic kidney disease impact the effectiveness of treatment.

The discovery of the role of receptor activator of nuclear factor-kappa b (RANK) ligand pathway in the regulation of osteoclast activity provided new treatment options for osteoporosis. RANK ligand-RANK interaction is required for differentiation of osteoclasts, and the absence of RANK ligand in humans and animal models leads to a phenotype of high bone mass [8]. Denosumab is a monoclonal antibody, RANK ligand inhibitor, registered for the treatment of osteoporosis, inhibits osteoclast formation function, and decreases bone resorption [9]. It is a subcutaneous injectable agent every 6 months.

In the multicenter randomized, double-blind Fracture Reduction Evaluation of Denosumab every 6 months (FREEDOM) trial, postmenopausal women aged between 60 and 90 years received 60 mg denosumab subcutaneous every 6 months for 3 years [10] and in extension study safety, and efficacy of denosumab was approved for 10 years [11]. Denosumab treatment significantly reduced vertebral and nonvertebral fracture risk, increased lumbar spine and total hip BMD, and reduced bone turnover markers, according to results of the FREEDOM study. BMD measurements were reported to be increased 9.2% in the L1–L4 area, and 6% in the hip were at the 36th month. In a 10-year continuation study, the cumulative BMD increase from the baseline was 21.7% at the lumbar spine and 9.2% at the total hip. Patients who discontinued denosumab treatment after 3–5 injections showed similar percentages of fracture rates; however, frequency of multiple vertebral fractures increased in the long term [11–14].

Denosumab also seems to be advantageous in the manner of adherence [15]. Clinical studies indicate advantages of subcutaneous 6-month interval denosumab according to oral bisphosphonates in postmenopausal women [15].

The effectivity in increasing BMD, decreasing bone turnover markers, and fracture risk was shown with randomized controlled studies; real-life setting is needed to be evaluated.

In this study, we aimed to determine denosumab treatment's persistence rates and effectiveness in a real-life setting for 2 years.

Material and method

The patients diagnosed with osteoporosis and prescribed denosumab treatment between 2014 and 2020 in our clinic were analyzed retrospectively from patient files and medical records. Demographic and clinical data fracture and medication history for osteoporosis were recorded. The total denosumab doses, denosumab injection time, treatment start and end, and missed doses were recorded. Side effects, fracture history under denosumab treatment, and following treatments for osteoporosis were obtained.

Persistance was evaluated as if the patient had the denosumab dose at time (time between two injections as 6 months ± 8 weeks).

World Health Organization diagnostic criteria were used to diagnose osteoporosis [17]. Available BMD measurements before and during treatment and lateral vertebra X-rays were evaluated. Bone mineral density was measured with GE Lunar DXA scanner.

The following laboratory data were obtained from patient files: serum calcium, phosphor, parathormone (PTH), 25(OH)D, osteocalcin, c-telopeptide (C-TX), alkaline phosphatase (ALP).

25(OH)D was measured by the paramagnetic particle chemiluminescence immunoassay method in serum samples (Beckman Coulter, USA). Intact parathormone levels were evaluated with immunoassay (Cobas 6000, Roche). Alkaline phosphatase was studied by colorimetric method, inorganic phosphate and calcium were studied photometrically (Beckman Coulter, USA), and osteocalcin and c-telopeptide were studied by chemiluminescence immunoassay.

Lateral vertebral graphics were reviewed by a radiologist blindly. The vertebral fractures were defined according to Genant's semi-quantitative method [16].

The categorical variables were presented as frequencies and percentages, whereas numerical variables were presented as median, IQR, minimum, and maximum values. The temporal changes in continuous variables were reported as percentages, where the selected measurements (numerator) were divided to baseline measurements (denominator) and multiplied with 100. The comparisons between two numerical dependent variables were performed with Wilcoxon signed-rank test. The comparisons among independent groups for numerical variables were executed with Mann–Whitney *U* test. The correlations between numerical variables were calculated with Spearman's test, where rho and *p* values were reported. All analysis were executed with

Stata 15.1 software (StataCorp, 4905 Lakeway Drive, College Station, Texas, 77,845, USA) and a p value less than 0.05 was considered statistically significant.

The local ethics committee approved the study protocol (09.2021.605).

Results

Three hundred and five patients (F/M: 275/30, 68.1 ± 11.05 years) received at least one dose of denosumab 60 mg subcutaneous included in the final analysis. The median dose that the patients had was 4 (1–10, IQR = 4). The characteristics of the patients included are shown in Table 1.

Two hundred seventy-three patients (89.8%) were persistent on treatment at the 12th month; 175 patients (57.3%) were persistent at the 24th month of denosumab treatment (Fig. 1). Thirty-one patients received only one injection, and 44 patients received only two injections in 1 year. One hundred thirty-six patients (44,5%) were still on denosumab treatment at the end of the second-year follow-up. Sixty-eight patients (22%) were not continuing denosumab. From these patients, 24 were switched after six doses of denosumab, and six patients were switched after ten doses to oral bisphosphatase with good response to treatment by doctor's recommendation. Sixteen patients were switched due to decreased BMD levels, and eight patients were switched due to fracture under treatment to intravenous bisphosphonates or teriparatide. Only in one patient treatment was stopped due to a side effect as an urticarial reaction observed after s.c denosumab injection. Twelve patients were switched to an alternative or discontinued treatment due to non-adherence or patients' demand for non-injectable treatment.

Fifty-five (%18) of the patients were stopped denosumab treatment by doctor decision, 12 (4%) were not continuing due to patient-related causes, and one patient was not continuing due to a severe side effect.

The remaining 101 patients' data that did not come to follow-up could not be reached from medical records.

Fifty-seven patients had fracture history at the beginning of treatment. Foty-five of them were nonvertebral. Eleven patients had hip fracture and 12 patients had vertebra fracture. Two hundred forty patients had a basal vertebral thoracolumbar x-ray. All of the evaluated patients had at least grade 1 vertebral fracture. One hundred thirty-three patients had grade 2 and worse fractures according to Genant's classification. The median fracture number was 3 [1–14].

90.1% of patients (n:275) were postmenopausal women. The male patients (n:30) were in minority because reimbursement covered only postmenopausal osteoporosis at that time.

The patients' median basal femur neck BMD values were 0.702 (0.349–0.997) g/cm^3 and the median L1–L4 BMD value was 0.809 (0.2–1.6) g/cm^3. Median femur neck and L1–L4 BMD values before and during treatment were shown in Figs. 2 and 3.

Seventy patients had type 2 diabetes mellitus. The basal femur neck BMD was 0.703 (0.349–0.954) and L1–L4 BMD was 0.839 (0.569–1.289). The mean increase in 12th month for femur was 0.021 (−0.059–0.306) ($p = 0.807$) and L1–L4 BMD was 0.029 (−0.115–0.229) ($p = 0.35$) of patients and were similar between with and without diabetes mellitus.

Fifty-four patients had a history of malignancy.Twenty-five patients had breast cancer history, six patients had hematologic malignancy, three patients had a history of lung cancer, two patients had nasopharynx cancer, five patients had gastrointestinal system malignancy, five patients had urogenital three patients had thyroid malignancy, and five patients had central nervous system malignancy. BMD increase for the femur ($p = 0.83$) and L1–L4 ($p = 0.42$) in 12 months of treatment was similar with patients without malignancy history.

Table 1 Demographic parameters and characteristics of patients

Sex (F/M)	275/30
Age (years)	68 (44–98, IQR = 16)
BMI (kg/m^2)	26.03 (15.59–44.63, IQR = 7.05)
Median dose	4 (1–10, IQR = 4)
Reason for admission to hospital	
Without complaint	176 (57.7%)
Back pain	63 (20.6%)
Bone pain	35 (11.4%)
Fracture	27 (8.85%)
Signs and symptoms	
Bone pain	224 (73.4%)
Back pain	230 (75.4%)
3 cm shortening of height	182 (59.6%)
Previous osteoporosis treatment (n,%)	178 (58.3%)
Zoledronic acid (n, %)	55 (18.03%)
Teriparatide (n, %)	35 (11.4%)
Oral bisphosphonate (n, %)	131 (42.9%)
Comorbidities and underlying causes	
Diabetes mellitus	70 (22.9%)
Hypertension	109 (35.7%)
Malignancy history	54 (17.7%)
Steroid history	54 (17.7%)
Chronic renal failure	37 (12.1%)
Coronary artery disease	19 (6.2%)
Romatoid artritis	18 (5.9%)
Hyperthyroidism	16 (5.24%)
Hyperparathyroidism	15 (4.91%)

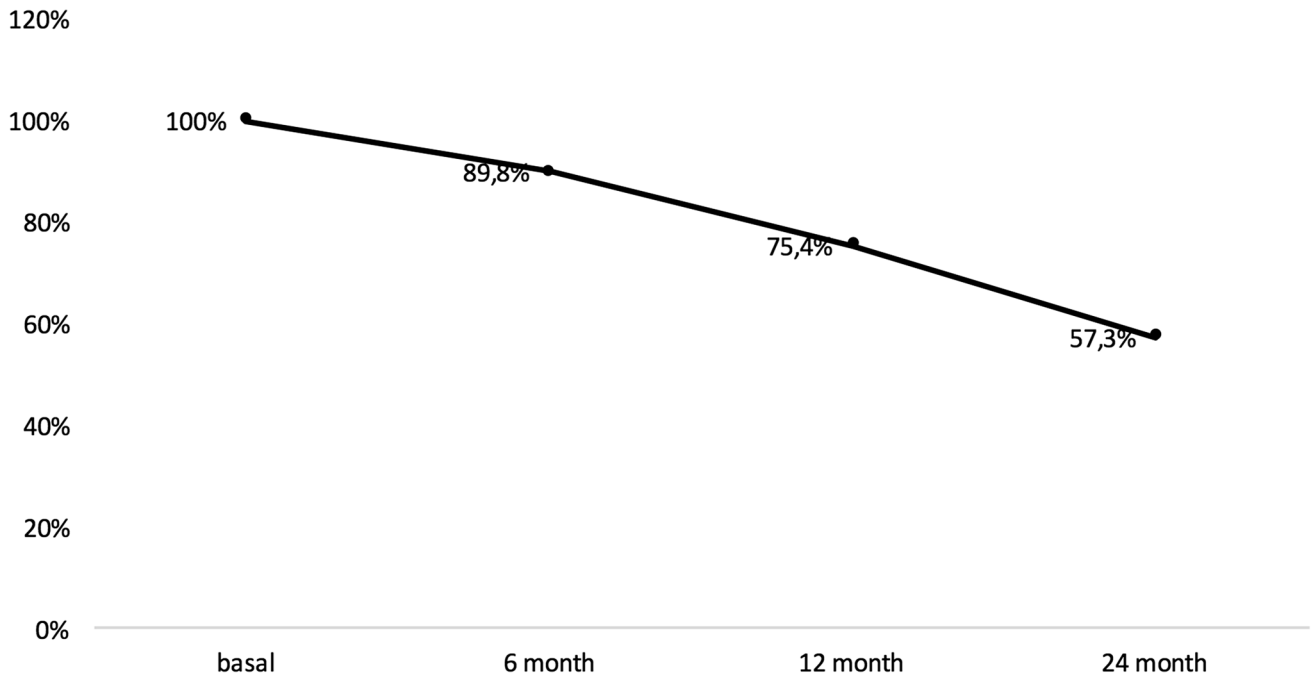

Fig. 1 Persistence of patients on denosumab treatment

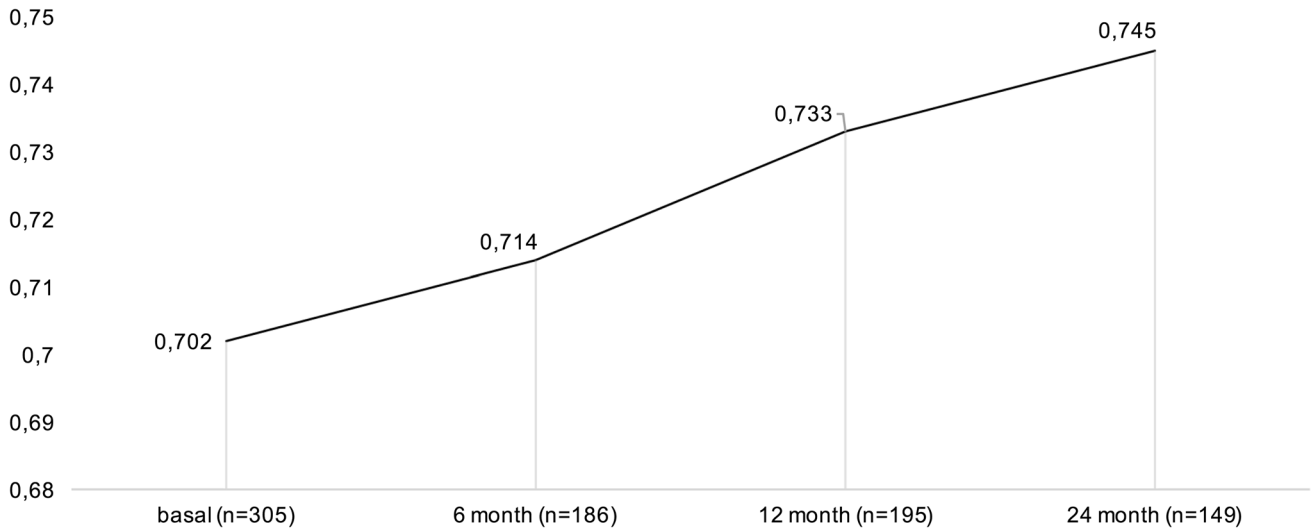

Fig. 2 Femur neck BMD levels of patients before and during treatment

Thirty-seven patients had stage 3–4 chronic renal disease history. The mean age and sex of the patients with and without chronic kidney disease were similar. The basal L1–L4 BMD was 0.879 (0.622–1.266); femur neck BMD was 0.701 (0.533–0.951). The BMD increase in the femur was 0.034 (−0.148–0.185) ($p=0.45$) and L1–L4 was 0.041 (−0.09–0.229) ($p=0.63$) in the 12th month of treatment was similar between patients with chronic renal disease and not.

When we evaluated the BMD levels of patients with steroid history, the BMD increase in the femur ($p=0.42$) and L1–L4 ($p=0.56$) were similar with patients without steroid history in the 12th month of treatment.

The median BMD change in femur neck in the 6th month was 0.017 (−0.186–0.303) g/cm^3 (2.5%) ($p<0.001$), in the 12th month 0.021 (−0.2–0.3) g/cm^3 (3.2%) ($p<0.001$), and in the 24th month 0.034 (−0.1–0.27) g/cm^3 (4.5%) ($p<0.001$) (Fig. 2).

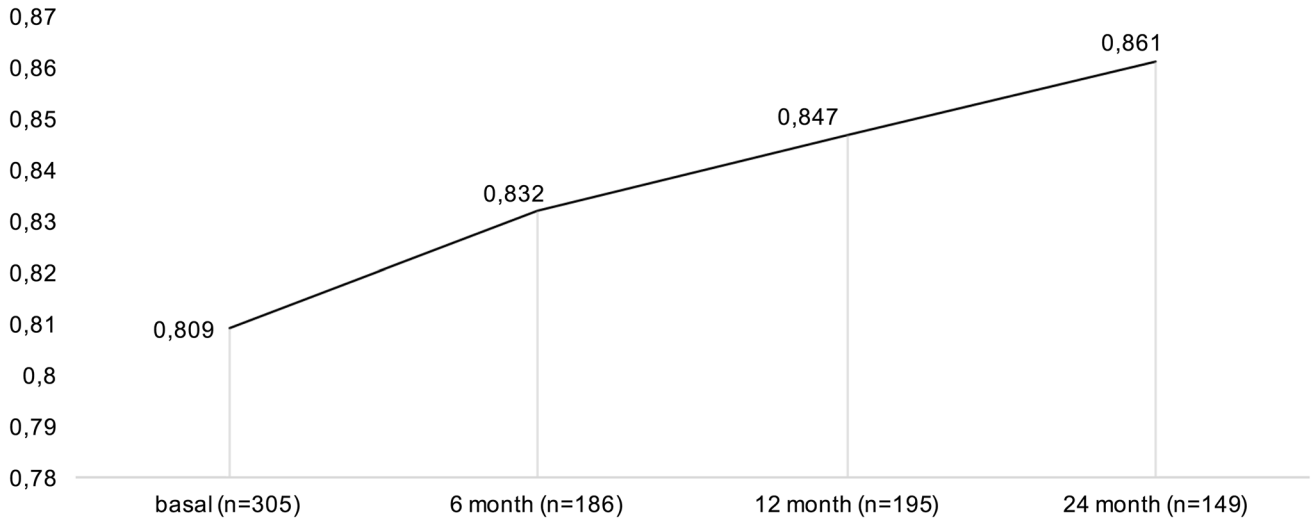

Fig. 3 L1–L4 BMD levels of patients before and during denosumab treatment

The median BMD change in L1–L4 at the 6th month was 0.0235 (−0.27–0.27) g/cm^3 (2.8%) ($p < 0.001$), in the 12th month 0.041 (g/cm^3 ($p < 0.001$) (4.8%), and in the 24th month 0.067 ± 0.064 g/cm^3 (8.04%) ($p < 0.001$). These improvements were significant statistically (Fig. 3).

The femur and L1–L4 BMD *t* scores were evaluated according to basal levels in sixth ($p < 0.001$, $p < 0.001$), 12th ($p < 0.001$, $p < 0.001$), and 24th ($p < 0.001$, $p < 0.001$) months. There were significant improvements.

The patients' baseline and follow-up laboratory parameters are shown in Table 2. When compared with the sixth month levels, there was a significant decrease in c-telopeptide ($p = 0.0085$), osteocalcin ($p < 0.001$), and ALP ($p < 0.001$) levels. There was no significant change in serum calcium, inorganic phosphate, parathormone, and 25(OH) D levels.

Basal femur neck (rho = 0.14, $p = 0.01$) and L1–L4 BMD (rho = 0.15, $p = 0.01$) levels had a weak significant positive correlation with BMI, but BMD increases in 6, 12, 24, and 36 months did not show correlation with BMI.

Eight patients (2.6%) had fractures under denosumab treatment. Two vertebral fractures, two femur fractures, three wrist fractures, and 1 humerus fracture were reported. Meantime to the fracture after the last denosumab dose was 5 months (3–6 months).

Discussion

In our retrospective cohort, we evaluated 305 patients who had at least one injection of denosumab. We observed an improvement of 8.04% in L1–L4 BMD and 4.5% in femur neck BMD levels at the 2nd year of treatment in persistant patients. These results were compatible with the results of FREEDOM study that 9.2% improvement in L1–L4 BMD and 6% in femur neck BMD was shown at the 36th month [10]. Also, similar results were shown in a real-life study from Ireland population. At 18th month of treatment, 8.4% increase in lumbar vertebra BMD and 3.5% increase in hip BMD were shown [17].

In this study, 89.8% of the patients had the treatment for at least 1 year; 57.3% were persistent on the 24th month. 33.4% of the patients were not on the follow-up. Sixty-eight patients were not continuing denosumab; 55 of them switched to another treatment with doctor recommendation. Thirty of these patients switched to oral bisphosphonate at 3rd or 5th year of treatment as the BMD levels were better according to basal levels. The persistence in this study was compatible with previous studies. In a study enrolled in the US and Canada, the persistence was 58% at the 24th month [18]. In a study, persistence for denosumab at the 24th month was 50% [19]. In another study also, treatment adherence was found to be 63.3% at the 24th-month evaluation [20]. In recent real-life persistence data about denosumab, persistence was 71% in a 7.5 year of follow-up, which was higher from other studies. The authors attributed this to positive motivation practices by describing the results of treatment with patients during outpatient control [21]. The osteoclastic effects of denosumab reverse with cessation of treatment and increase in fracture risk was shown with studies [13, 14]. In the light of these studies, follow-up of the patients and informing the patient about the risks that the patient may face in case of discontinuation of treatment is an important issue for the treatment success.

Denosumab is a well-tolerated drug and attractive due to the twice-yearly dosing schedule for drug compliance. According to the results of FREEDOM study, denosumab did not lead to an increase in the risk of cancer, infection,

Table 2 Laboratory parameters of patients before and after denosumab treatment

		Before denosumab	6th month	12th month	24th month
Calcium	Median	9.6	9.6	9.7	9.8
	Min–max	8.3–11.6	8.5–11.6	8.5–11.7	8.7–11.8
	IQR	0.7 ($n=302$)	0.6 ($n=254$	0.7 ($n=217$)	0.5 ($n=168$)
Inorganic phosphate	Median	3.2	3.3	3.4	3.3
	Min–max	1.4–5.9	1.91–6.1	1.84–5.6	1.1–5.9
	IQR	0.7 ($n=300$)	0.80 ($n=250$)	0.71 ($n=210$)	0.98 ($n=164$)
Parathormone	Median	49	55.7	48	48
	Min–max	15–194	11–273	12–365	12–300
	IQR	34.2 ($n=287$)	39 ($n=230$)	33.8 ($n=208$)	32.4 ($n=162$)
25(OH)D	Median	32	33	32	32
	Min–max	8–144	6–89	11–80	13–106
	IQR	15.5 ($n=271$)	13.3 ($n=215$)	16.1 ($n=187$)	14.9 ($n=148$)
C-TX*	Median	0.43	0.15	0.16	0.2
	Min–max	0.05–2.56	0.06–1.15	0.06–1.05	0.03–1.34
	IQR	0.39 (n: 77)	0.23 ($n=54$)	0.18 ($n=53$)	0.21 ($n=73$)
Osteocalcin#	Median	5.14	2.44	2	2
	Min–max	0.7–62.6	2–13	2–13	2–14.7
	IQR	7.04 (n: 97)	1.26 ($n=77$)	0.80 (79)	0.72 (84)
ALP**	Median	79	65	62	64
	Min–max	33–221	19–168	13–263	20–252
	IQR	41 ($n=113$)	29.2 ($n=60$)	17 ($n=53$)	28 ($n=66$)

*Basal CTX vs 6th month CTX $p=0.0085$, #basal osteocalcin vs 6th month osteocalcin $p<0.001$, **basal ALP vs 6th month ALP $p<0.001$

cardiovascular disease, hypocalcemia, or jaw osteonecrosis [10]. In this current study, a side effect caused drug discontinuation only in one patient as urticaria, which was thought to be due to denosumab. There was only one case report in literature about the side effect of denosumab as urticaria [22]. There was no recorded hypocalcemia or jaw osteonecrosis in the patients' medical records. Nevertheless, as this study was a retrospective study and as the primary outcome was not the side effects and follow-up of the patients was not planned according to side effect profile, this study could not give detailed information about the side effect profile.

At the beginning of denosumab treatment, fifty-seven patients had fracture history but according to vertebral x-ray evaluation; 133 patients had grade two or worse fractures. The evaluation of vertebral x-ray is very important for undiagnosed fractures and treatment decision.

According to results of this study, 2.6% of patients had fracture under deosumab treatment which is compatible with the results of a real-life study of a large cohort from China, with a total fracture number of 591 in 13,419 patients (4.4%) and results of the randomized controlled FREEDOM study (0.9–1.6% vertebral fracture and 0.84–2.55% nonvertebral fracture) [11, 23].

In this study, 37 patients had stage 3 or 4 chronic kidney disease. The improvement in BMD levels of these patients was similar to patients with normal renal function and there was no increased hypocalcemia as a side effect in this group. The studies in the literature also confirm the effectiveness of denosumab to increase BMD levels in chronic kidney disease [24, 25]. Also, according to the results of this study, denosumab is equally efficient and safe in diabetic patients, patients with malignancy history, patients with steroid history, and patients with chronic renal disease in real-life setting.

In conclusion, this is the first study of real-life results of denosumab treatment in osteoporotic Turkish population in real-life setting of denosumab treatment. These studies further give information about drug adherence and effectiveness in the real-life setting [19–21, 26]. According to the results of this current study, denosumab is an effective

treatment for osteoporosis with similar effectivity in different comorbid conditions with non-significant side effects. The follow-up of the patients with laboratory and DXA results is essential to evaluate the clinical outcomes of the treatment and maintain treatment adherence. The treatment switch with the physician's decision also seems to be an essential factor for treatment discontinuation, and physician awareness can be increased that denosumab is a safe drug with a favorable adherence.

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Data availability The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Conflicts of interest None.

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