Original Article

Comparative effects of denosumab or bisphosphonate treatment on bone mineral density and calcium metabolism in postmenopausal women

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Abstract

Objectives: To clarify potential differences between denosumab (DNS) and bisphosphonates (BIS) in terms of bone density and bone metabolism, in a sample of postmenopausal women. **Methods:** A total of 113 postmenopausal women aged 53-66 years were treated with either DNS or BIS for 12 months. Bone densitometry and laboratory tests were compared between baseline and follow-up. **Results:** Femoral neck BMD increased in both treatment-arms (FN-BMD, DNS: 0.69 ± 0.07 g/cm^2 to 0.75 ± 0.09 g/cm^2; BIS: 0.69 ± 0.06 g/cm^2 to 0.71 ± 0.07 g/cm^2; $p\leq0.001$ in both cases). Lumbar spine BMD (LS-BMD) increased significantly only in the DNS-group (0.83 ± 0.14 g/cm^2 to 0.89 ± 0.14 g/cm^2, p=0.0001). Only women under treatment with DNS had a significant increase in serum parathyroid hormone (PTH: 44.87 ± 17.54 pg/mL to 53.27 ± 15.77 pg/mL, p=0.04), independently of baseline vitamin D levels. DNS-administration resulted in higher increase from baseline in FN-BMD compared to BIS (DNS vs BIS: $8.7\%\pm8.5$ vs $3.8\%\pm7.3$, p=0.004). Finally, baseline 25OH vitamin D levels did not determine the extent of PTH-increase following administration of DNS- or BIS-treatment. **Conclusions:** Both treatments increased BMD, however, the effect of DNS on FN-BMD was superior compared to that of BIS. DNS-treatment increased serum PTH. Baseline 25OH vitamin D levels did not predict the extent of PTH increase at follow-up.

Keywords: Bisphosphonates, Denosumab, Postmenopausal Osteoporosis

Introduction

Pharmacological intervention for osteoporosis primarily targets the bone resorption component of bone remodelling pathways, through the administration of anticatabolic or antiresorptive agents[1]. Among currently available agents, bisphosphonates and denosumab are widely used as first line treatment for osteoporosis. The only anabolic agents currently available are teriparatide or the intact parathyroid hormone molecule which are generally considered as second line therapy reserved for severe cases[1].

Bisphosphonates, the traditional antiresorptive agents, exert an inhibitory effect on osteoclasts, reducing thus bone resorption[2]. A large body of evidence has confirmed

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Appendices	
PTH = parathyroid hormone	
25-OHD = 25-hydroxyvitamin D	
BMD = Bone mineral density	
BMI = Body Mass Index	
RANKL = Receptor activator of nuclear factor kappa-B ligand	

their efficacy in preventing the development of vertebral, hip and non-vertebral fractures, as well as in reducing fracture-related mortality among high-risk patients[3-5]. Two widely used bisphosphonates as first-line treatment options are those we used in this study, the oral alendronate and the intravenously administered zoledronic acid. They are nitrogen-containing bisphosphonates[6], which target a specific metabolic enzyme, farnesyl pyrophosphate synthase, preventing the normal modification of intracellular proteins required for osteoclast function and survival[2,6,7].

Denosumab is a human monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL), a cytokine with a central role in bone remodeling, affecting thus adversely recruitment, maturation and action of the cells of the osteoclast lineage[8,9]. Denosumab is indicated for postmenopausal women with either high fracture risk or for women experiencing failure of a previous anti-osteoporotic treatment regimen or women not tolerating other available types of anti-osteoporotic therapy[9]. The use of bisphosphonates for the treatment of postmenopausal osteoporosis reduces the risk of osteoporotic fractures and stabilizes or increases bone mass and strength[3].

Meta-analyses comparing the impact of antiresorptive agents on bone metabolism indicate an overall greater effectiveness of denosumab vs bisphosphonates in a clinical setting[10,11]. However, recent data indicated an association between both denosumab or alendronate administration and the development of hypocalcemia[12,13], whereas comparative clinical data of these two regimens are still sparse.

This retrospective follow up study aims to trace differences between bisphosphonates and denosumab treatment in a sample of women with postmenopausal osteoporosis, concerning bone densitometry and calcium metabolism.

Materials and methods

Subjects

A total of 113 postmenopausal women aged 53-66 years were included in this retrospective follow-up study. The menopausal status was defined as follicle stimulating hormone >25 mIU/mL and estradiol <50 pg/mL, after 12 consecutive months without menses. Subjects were recruited from the Menopause Clinic of the 2nd Department of Obstetrics and Gynecology, National and Kapodistrian University of Athens, Aretaieio Hospital. This Clinic, active since 1998, serves both symptomatic and asymptomatic middle-aged women, providing information about menopause and offering screening and risk assessment for major morbidities of midlife and beyond, such as osteoporosis, cardiovascular disease, cervical and breast cancer. A detailed electronic file is built for each informed-consenting woman containing demographic, life-style and anthropometric parameters as well as biochemical and hormonal assessments according to individual needs.

Inclusion was based on the following criteria: 1) the presence of postmenopausal osteoporosis, as defined by T-score <-2.5 either in the lumbar spine or the femoral neck or the presence of an osteoporotic fracture, 2) the absence of secondary causes of osteoporosis and 3) the use of either denosumab (60 mg sc every six months) or a bisphosphonate (alendronate 70 mg p.o. once weekly or zoledronic 5 mg acid IV once annually) for at least 12 months. All women received advice on complementary treatment with calcium and vitamin D supplements (1000 mg/ 800 IU/ day). Data were retrieved from the database of our Clinic and concerned the baseline visit, before the initiation of the medication and the 12 month visit post-treatment. Women signed an informed consent for the use of their data for statistical analysis and the Study was approved by the Ethics Committee of the Aretaieio Hospital.

Anthropometric measurements

Weight and height were measured in the morning and in light clothing in order to estimate the Body Mass Index (BMI). Weight was measured on an electronic scale and height was measured in a stadiometer in the upright position. BMI was calculated using the equation BMI= body weight (kg)/height^2 (m^2).

Bone densitometry

Bone mineral density (BMD) of the lumbar spine and left femur was measured at three sites (L2, L3 and L4) by dual energy absorptiometry (DXA; Excell Plus, Norland Corp, Arm Model 433A063) and expressed as the amount of mineral (g) divided by the area scanned (cm^2). All DXA measurements were performed by the same densitometer. Using the Mediterranean database provided by the densitometer, T-scores (number of SD below peak bone mass) and Z-scores (number of SD below age and sex-matched controls) were calculated for L2, L3, L4 and total lumbar spine (L2–L4). In adults, osteopenia and osteoporosis were determined according to the World Health Organization operational BMD definition for these terms. Osteoporosis was defined as a BMD T-score at any site less than -2.5, and osteopenia was defined as a BMD T score between -1 and -2.5.

Laboratory evaluations

Serum levels of total calcium, phosphate as well as 25-hydroxyvitamin D (25-OHD) and parathyroid hormone (PTH) were assessed enzymatically by an autoanalyzer (ARCHITECT ci4100 Integrated System, Abbott Diagnostics Laboratories, Abbott Park, IL 60064, USA, and Abbott, 65205 Wiesbaden, Germany). According to our laboratory, the reference values range as follows (using the following normal ranges): calcium (8.4-10.2 mg/ dL), phosphate (2.4-4.1 mg/dL), serum 25-hydroxyvitamin D (25-OHD, 30-74 ng/mL) and parathyroid hormone (PTH,10-61 pg/ mL). Vitamin D deficiency was defined as serum levels ≤10 ng/mL, while serum levels of vitamin D≤20 ng/mL were defined as suboptimal[14].

Table 1. Baseline demographic characteristics of 113 postmenopausal women participating in the study.

	Denosumab (n=51)	Bisphosphonates (n=62)	P Value*
Continuous variables			
Age (years)	60.41(6.2)	58.50(5.9)	0.14
Years since menopause	11.25(6.5)	10.26(6.3)	**0.42**
BMI	25.99(3.5)	26.42(6.4)	**0.84**
Weight	64.42(8.042)	66.11(9.31)	**0.46**
Mean blood pressure	92.99(14.25)	96.84(10.68)	**0.09**
Categorical Variables (%)			
Current smoking	28.8	31.7	0.86
Diet rich in calcium*	21.1	24.5	0.18
Alcohol (daily)**	9.6	14.2	0.44
Physical exercise (>3h/week)***	19.2	15.8	0.72
*Diet rich in calcium (at least 2 glasses milk or two yogurts or 75-100 gr cheese every day). **At least 15 g per day alcohol which is 1 glass 5 oz (148 mL) of wine or beer. ***Different types of mild aerobic exercise. Statistical significance was set at the level of p<0.05.*			

Statistical analysis

Statistical analysis was performed by SPSS Version 21 (Statistical Package for the Social Sciences, Chicago, IL, USA). Baseline comparisons between groups were performed by Student's t-test for unpaired observations concerning continuous variables and by X-square concerning categorical variables. Skewed variables were log-transformed before entered in the analysis. Baseline and follow up bone density parameters mean levels were compared within therapy groups by t test for paired observations. Percent changes in outcome variables were compared between groups with Student's t-test for unpaired observations. Non-parametric tests were used in cases where the distribution deviated significantly from normality. The impact of both treatment arms on bone density and calcium metabolism was further evaluated, comparing subjects according to baseline levels of 25OHD. Statistical significance was set at the 0.05 level.

Results

Mean levels of baseline demographic parameters are presented in Table 1. No difference between the two treatment groups was detected with respect to age, years since menopause, BMI, weight, current smoking, diet, alcohol consumption or physical exercise. 23.8% of women under denosumab and 22.2% of women under bisphosphonates had suboptimal levels of vitamin D at baseline. The difference between the two treatment arms was not statistically significant.

Baseline and follow-up mean levels of BMD and T-scores in spine and femoral neck, calcium, phosphate, PTH and 25-hydroxyvitamin D, are presented in Table 2. Baseline values concerning all assessed parameters did not differ between the two treatment groups. Both treatments resulted in significant increases in femoral neck BMD (denosumab 0.69 ± 0.07 g/cm^2 to 0.75 ± 0.09 g/cm^2 p=0.0001, bisphosphonates 0.69 ± 0.06 g/cm^2 to 0.71 ± 0.07 g/cm^2 p=0.001). Lumbar spine BMD increased significantly in the denosumab group (0.83 ± 0.14 g/cm^2 to 0.89 ± 0.14 g/cm^2 p=0.0001) and marginally significantly in the bisphosphonate group (0.84 ± 0.10 g/cm^2 to 0.87 ± 0.11 g/cm^2 p=0.09). Denosumab was associated with a significant increase in serum PTH (44.87 ± 17.54 pg/mL to 53.27 ± 15.77 pg/mL p=0.04), an effect not observed in the bisphosphonate group (45.79 ± 14.74 pg/mL to 49.64 ± 20.67 pg/mL p=0.25). No changes in serum calcium, phosphate or 25OHD were observed in either of the two treatment groups.

Percent changes from baseline in the two study groups concerning BMD in the lumbar spine and femoral neck are presented in Figure 1. Denosumab resulted in significantly higher increase in femoral neck BMD compared to bisphosphonates (denosumab 8.7%±8.5, bisphosphonates 3.8%±7.3, p=0.004). The same was apparent for lumbar spine BMD, the difference, however, did not reach statistical significance (denosumab 9.03%±11.3, bisphosphonates 4.5%±11.6, p=0.154). In accordance, T-score increases were higher in the denosumab group compared to the bisphosphonate group, the difference being significant only for femoral neck (% change T-score femoral neck: denosumab 21.2%±20.14, bisphosphonates 7.43%±17.4, p=0.003; % change T-score lumbar spine: denosumab 12.4%±23.0, bisphosphonates 6.3%±29.2, p=0.91). No significant differences between changes in the two groups were observed concerning the biochemical parameters.

Further evaluating the impact of both treatment arms on calcium metabolism, we compared changes in PTH levels throughout the treatment period according to baseline levels of vitamin D. With respect to denosumab, we observed that the increase in PTH levels was similar between women with suboptimal and optimal 25OH vitamin D levels at base-
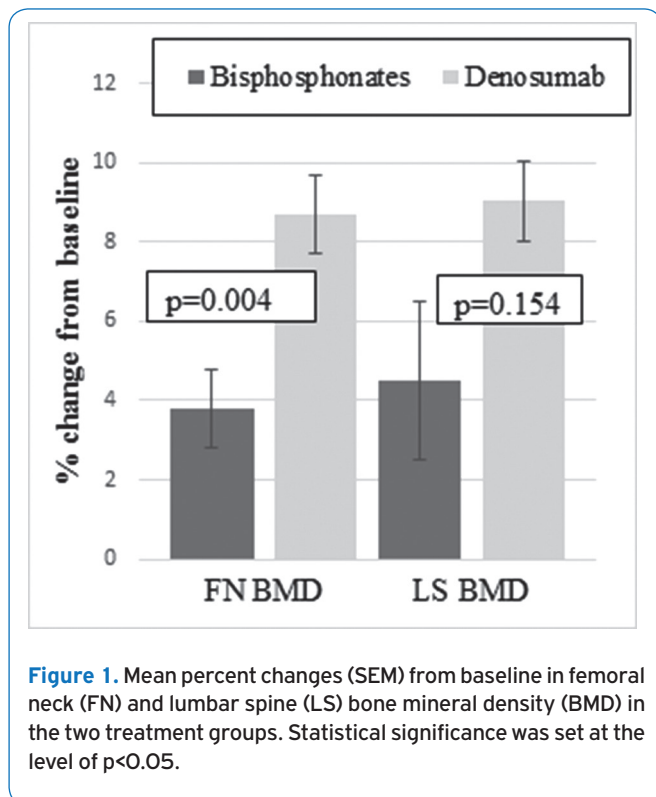
Table 2. Baseline and follow-up mean (SD) values of bone mineral density (BMD) and laboratory parameters in the two treatment groups.

	Months	Denosumab (n=51)	Bisphosphonates (n=62)	p Value*
BMD lumbar spine	0	0.83(0.14)	0.84(0.10)	0.77
	12	0.89(0.14)	0.87(0.11)	
	p Value**	0.0001	0.09	
BMD femoral neck	0	0.69(0.07)	0.69(0.06)	0.98
	12	0.75(0.09)	0.71(0.07)	
	P Value	0.0001	0.001	
T score femoral neck	0	-2.34(0.59)	-2.47(0.56)	0.54
	12	-1.90(0.74)	-2.27(0.59)	
	P Value	0.0001	0.0014	
Calcium	0	9.59(0.48)	9.42(0.53)	0.18
	12	9.59(0.49)	9.45(0.45)	
	P Value	0.91	0.84	
Phosphate	0	3.45(0.5)	3.55(0.45)	0.16
	12	3.27(0.5)	3.45(0.45)	
	P Value	0.02	0.13	
Parathyroid Hormone (PTH)	0	44.87(17.54)	45.79(14.74)	0.82
	12	53.25(15.77)	49.64(20.67)	
	P Value	0.04	0.25	
25OH Vitamin D	0	28.82(11.66)	25.10(12.10)	0.12
	12	31.09(8.89)	26.11(12.41)	
	P Value	0.14	1	

*: p value, t-test for unpaired observations, comparisons between baseline values of the two treatment groups.
**: p value, t-test for paired observations, comparisons within treatment group.
Statistical significance was set at the level of p<0.05.

Figure 1. Mean percent changes (SEM) from baseline in femoral neck (FN) and lumbar spine (LS) bone mineral density (BMD) in the two treatment groups. Statistical significance was set at the level of p<0.05.

line (women with 25OH vitamin D <20 ng/ml: 34.3±68.1% increase, p=0.284; women with 25OH vitamin D ≥20 ng/ml 26.3±57.7% increase, p=0.120). Similarly no effect of baseline 25OH vitamin D levels was seen in women under bisphosphonate treatment (women with 25OH vitamin D <20 ng/ml: 23.8±19.9% increase, p=0.266; women with 25OH vitamin D ≥20 ng/ml 2.34±22.2% increase, p=0.527).

Discussion

Our study showed that BMD at the femoral neck was significantly improved by both denosumab- and bisphosphonate-treatment, the impact of denosumab, however, was more pronounced compared to bisphosphonates. Denosumab improved significantly BMD at the lumbar spine after 12 months of treatment. Considering calcium metabolism, denosumab was associated with an increase in circulating PTH, independently of baseline levels of 25OHD.

In this study, denosumab resulted in a higher increase of BMD at all evaluated skeletal sites compared to bisphosphonates, with the effect being more pronounced in the femoral neck. These findings are in accordance with those of other studies. The results of large randomized controlled trials have already shown greater improvement of total BMD in

postmenopausal women under treatment with denosumab vs alendronate[15,16]. Moreover, denosumab may prevent more effectively structural skeletal decomposition, attributed to bone remodeling, compared to alendronate[16]. The impact of denosumab seems to be more pronounced on the cortical bone, affecting both BMD measures and micro-architecture, as estimated by studies that implemented high-resolution peripheral quantitative computed tomography[16]. However, whether this difference in surrogate markers can also be extrapolated to fracture rate remains uncertain.

Analysis of ongoing long-term studies suggests that denosumab has a continuous beneficial effect on bone density compared to certain types of bisphosphonate, like zoledronic acid, in which bone density gain reaches a plateau[17,18]. In the open-label extension of the pivotal FREEDOM trial, denosumab treatment for up to 8 years induced continued increases in BMD by DXA at the lumbar spine and total hip with the final changes from baseline being 18.4% at the lumbar spine and 8.3% at the total hip[17]. A pattern of progressive increase only in spine BMD has been observed in patients over 10 years with alendronate and 7 years with risedronate treatment, although the magnitude of the response with denosumab appears to be greater than with those antiresorptive agents[19,20]. Several mechanisms might explain the differential impact of denosumab on hip BMD. Firstly, the inhibitory effect of denosumab on bone resorption is more potent than bisphosphonates[21,22]. Secondly, the onset of action is rapid in individuals treated with denosumab, followed by a gradual release of the inhibitory effect over the 6-month period before the next dose. On the contrary, administration of bisphosphonate is related with varying onset and delayed offset of action, according to the individual agent[9]. Finally, the pharmacokinetics of denosumab seems to result into recovery of bone remodelling capability at the end of each cycle of therapy. New spaces of bone tissue go through the process of bone remodelling but fail to undergo resorption under the inhibitory impact of the next dose of denosumab[18]. These effects might lead into a more positive balance in bone turnover, as observed in women under treatment with denosumab compared to bisphosphonate.

In this study, denosumab was associated with a significant increase in serum PTH, an effect not observed in the bisphosphonate group. This finding is consistent with the results of two previous clinical studies, according to which the increase in circulating PTH occurs early, within the first 15 to 30 days following denosumab administration and persists, albeit attenuated, for six months[23,24]. In the present study, however, the effect of denosumab on PTH was evident after 12 months of treatment. Further supporting our findings, a recent study[25] compared the effect of denosumab and alendronate on bone turnover, evaluating a sample of mature ovariectomized cynomolgus monkeys (cynos), for a period of 12 months. This study[25] identified a greater increase in serum PTH levels in cynos receiving denosumab compared to alendronate, at least during the initial 6-month period. Interestingly, the most robust PTH increase was observed in cynos who transitioned immediately to denosumab-treatment, compared to cynos who received prior treatment with alendronate[25], indicating the de-

termining effect of previously administered treatment on bone metabolism. Moreover, we observed that the increase in circulating PTH was not associated with levels of 25OH-vitamin D before the initiation of denosumab. This observation could be attributed to the low compliance to calcium supplements intake of our population. Makras et al. (2013) evaluated a sample of 47 postmenopausal women with normal baseline levels of 25OH-Vitamin D for 6 months. This study showed that high dose calcium and vitamin D treatment, up to 2 gr/1600 IU respectively even for 1 month might prevent the increase in PTH in women treated with denosumab[23].

Physical exercise has well known beneficial effects on bone metabolism. Multi-purpose exercise programs have shown favourable effects on bone metabolism, reducing the risk of fracture in postmenopausal women, as reported in the final results of the Erlangen Fitness and Osteoporosis Prevention Study (risk ratio for overall low-trauma fractures, exercise group vs controls 0.51; 95% CI: 0.23 to 0.97, p-value=0.046)[26]. Moreover, even short-term aerobic exercise can improve functional fitness and reduce bone resorption in women with low bone mass[27]. In this study, the percentage of women who underwent regular aerobic exercise was relatively low (19.2% vs 15.8%, for women under treatment with denosumab and bisphosphonates, respectively). Consequently, the sedentary lifestyle of the majority of our women may have accelerated the reduction in bone density[28], and may have compromised the response to the administered treatment.

Limitations of this study should be mentioned. First of all, the small sample size prohibited us from further exploring the effect of other potential confounders on the association between denosumab and parathyroid hormone. Secondly, the observational design of the study may have introduced unintentional biases. It should be mentioned, however, that the baseline characteristics were identical between the two study groups. Finally, we have not evaluated levels of bone turnover markers.

Concluding, denosumab in our study resulted in higher increases in BMD, especially at the femoral neck, compared to bisphosphonates. Denosumab treatment furthermore resulted in an increase of serum parathyroid hormone. Further clinical studies are required to evaluate whether more intense vitamin D and calcium supplementation can prevent the increase in PTH, following denosumab administration.

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