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Original research article

Effect of Subcutaneous Administration of Denosumab in Postmenopausal Osteoporosis

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Abstract

Introduction: Postmenopausal osteoporosis is a major health problem in Indian women as it increases chances of both vertebral and non-vertebral fractures. The benefits of the standard treatment regimen for prevention of postmenopausal osteoporosis are not encouraging. Denosumab, in various international studies is found as an effective treatment modality for prevention of postmenopausal osteoporosis. However, there is scarcity of data of Indian postmenopausal women. Therefore, present study is an attempt to observe the treatment effect of denosumab for prevention of postmenopausal osteoporosis.
Objective: To observe the treatment effect of denosumab in patients suffering from postmenopausal osteoporosis in terms of bone mineral density(BMD).
Methods: This randomized control study was done in 62 randomly selected patients with postmenopausal osteoporosis at SMS Hospital, Jaipur. After administering denosumab (60 mg every 6 months), we measured lumbar spine, total hip and distal radius BMD at 6 and 12 months.
Results: At 6 months, lumbar spine BMD increased more in denosumab group(0.29±0.17, P<0.001) compared to control group(0±0.29, P<0.001) and at the end of 12 months also, lumbar spine BMD increased more in denosumab group(0.56±0.24, P<0.001) compared to control group(-0.03±0.41, P<0.001). Similarly, at 6 months, total hip BMD increased more in denosumab group(0.38±0.23, P<0.001) compared to control group(-0.08±0.22, P<0.001) and at the end of 12 months, total hip BMD increased more in denosumab group(0.82±0.3, P<0.001) compared to control group(-0.1±0.36, P<0001). At 6 months, distal radius BMD increased more in denosumab group(0.27±0.25) compared to control group(0.00±0.37) and at 12 months, distal radius BMD increased more in denosumab group(0.58±0.34) compared to control group(-0.04±0.43).
Conclusions: Denosumab is effective to treat postmenopausal osteoporosis and it is more effective at hip than at lumbar spine and radius. To conclude further treatment is needed as sequential therapy because on stopping the treatment BMD again start receding over the period.
Keywords: Denosumab, Postmenopausal women, Bone mineral density, Osteoporosis

Introduction

WHO operationally defines osteoporosis as bone density that falls 2.5 SD below the mean for young healthy adults of same gender (t score≤ 2.5).[1,2] Postmenopausal osteoporosis occurs due to oestrogen deficiency which leads to decrease in IL-6 and other cytokines, which in turn leads to increased recruitment and activation of osteoclasts.[1] Postmenopausal osteoporosis is a major health problem in Indian women as it increases chances of both vertebral and non-vertebral fractures and the numbers are increasing.[3] Presently treatment seeking behaviour of patients in India is very poor and treatment offered for postmenopausal symptoms does not include effective prevention of postmenopausal osteoporosis.Today DEXA(dual energy x-ray absorptiometry) is the most widely used instrument and gold standard of bone mineral density measurement technology. Main advantages of DEXA are it is a non-invasive and a quick procedure with high accuracy and ideal for follow-up investigations. The disadvantage of DEXA is that everything in the selected area is included like presence of spinal osteophytes and aortic calcification which may give false readings. The benefits of the standard treatment guidelines for prevention of postmenopausal osteoporosis are not encouraging. Denosumab is a monoclonal human IgG2 antibody that inhibits RANKL from binding to its receptor RANK and it inhibits osteoclastic bone resorption (to a lesser degree bone formation) and it has been found effective in preventing osteoporosis in many international studies.[2,4,5]

OBJECTIVES: To observe the treatment effect of denosumab in patients suffering from postmenopausal osteoporosis in terms of bone mineral density i.e. t-score (by Hologic Qdr-delphi dual energy x ray absorptiometry) at 0, 6 and 12 months.

MATERIAL AND METHOD: Present prospective randomized control study was conducted between June,2019 to September 2020 in the department of PMR, SMS hospital, Jaipur among Established osteoporotic postmenopausal elderly patients aged 45 to 80 years with BMD t- score of -2.5or less at femoral neck / total hip OR lumbar spine BMD t- score of -1.5 to -2.5 at any site plus one or more documented vertebral or non vertebral fracture. Patients of renal dysfunction, hypocalcemia, hypercalcemia were excluded along with patients taking any medication for osteoporosis like denosumab, teriparatide, bisphosphonates, strontium. Permission from institutional ethics committee and research review board was obtained. 62 patients fulfilling criteria and giving consent to the study were included in the study and randomized into control and denosumab group using computer generated random numbers from www.random.org. All recruited 62 patients were approached by investigators and were explained about nature and purpose of the study. After obtaining their informed written consent, detailed history, thorough general & systemic examination was done. All baseline rutine investigations and specific investigatins like DEXA scan, vitamin D3 was done. In intervention group injection denosumab 60 mg subcutaneously was given in 1st and 7th month along with standard care including vitamin D3 60k once weekly, calcium supplementation, physical exercises whereas in control group only standard care given. Patients were followed up at 6 months and 12 months for repeat DEXA scan and injection denosumab repeat in intervention group. All relevant parameters collected during history taking, examinations & during routine and specific investigations at baseline, 6 months & 12 months were recorded as a pre-design semi-structured study proforma.

Data thus collected was entered in Microsoft excel sheet to prepare master chart and then subjected to statistical analysis.

Data analysis:
Linear variables were summarised as mean & standard deviations and were analysed using unpaired t-test and repeated measure annova.
Nominal and categorical variables were presented as percentages and were analysed using Chi-square test & Fisher exact test.
p-value ≤ 0.05 was taken as significant. SPSS 22.0 version software was used for statistical analysis.

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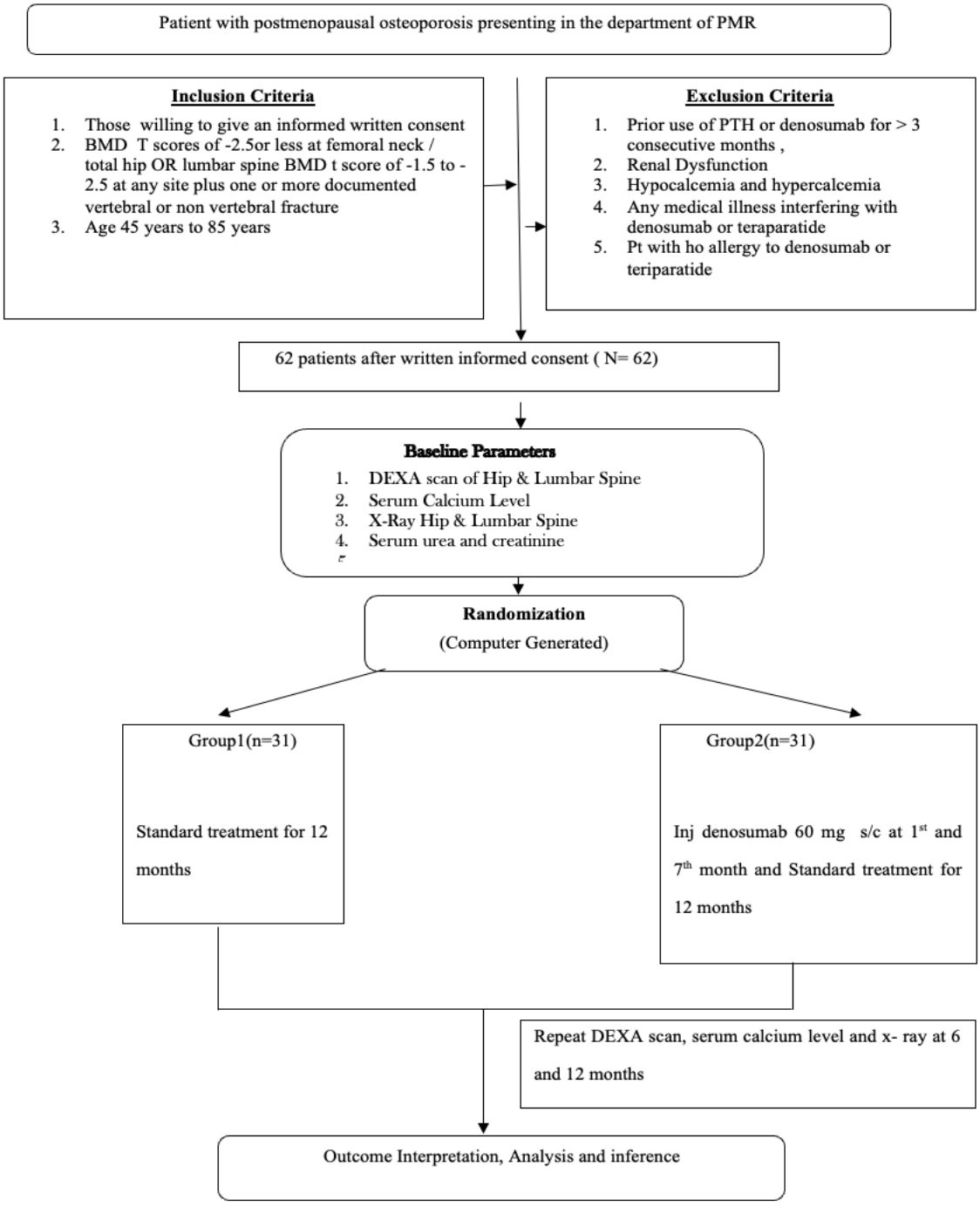


RESULTS:

Present study included 62 study participants who fulfilled inclusion critera and completed 12 months follow up period. Mean age and mean BMI of study participants were 61.97±9.48 years and 24.72±4.11 kg/m^2.

When patients were randomized into denosumab and control group, mean age and BMI of patients of denosumab group was 61.23±8.97 years & 24.94±4.30 kg/m^2 respectively and that in control group was 62.71±10.06 years & 24.5±3.97 kg/m^2 respectively. Mean age and BMI along with other general characteristics of patients was found comparable ($p>0.05$) between the groups (table 1).

When intra-group comparison of t-score of spine, hip & radius was analysed using repeated measure annova test, significant improvement ($p<0.05$) was observed in denosumab group at all 3 sites i.e. spine, hip & radius while in control group there was no significant change in t-score was found at any of the 3 sites(table 2).
Mean t-score of spine in denosumab group was -2.78, -2.49 & -2.22 at baseline, 6 months and 12 months respectively whereas it was -3.16, -3.16 & -3.19 at baseline, 6 months and 12 months respectively in control group. T-score of spine was found statistically signifcantly higher at 6 months & 12 months than control group, but not at baseline (table 3). Simlarly, t-score of hip joint in denosumab group was significantly higher at 12 months than control group but not at 6 months and baseline(table 3). Mean t-score of radius in denosumab group was found statistically significantly higher at 6 months and 12 months than control group, but not at baseline(table 3).

When difference in difference analysis was done to compare improvement or change in t-score after 6 months treatment duration and 12 months treatment duration, it was found that improvement was always higher in denosumab group than control group both after 6 months and 12 months treatment duration at all 3 sites i.e. spine, hip and radius (table 3).

Table 1 : General characteristics of Study Participants

	Total (N=62)		**Control (N=31)**		**Denosumab (N=31)**		**'p' value***
Age group (Years)	**No.**	**%**	**No.**	**%**	**No.**	**%**	
<50	6	9.7	4	12.9	2	6.5	0.813#
50-59	20	32.3	9	29.0	11	35.5	
60-69	21	33.9	9	29.0	12	38.7	
≥70	15	24.2	9	29.0	6	19.4	
PMP period							
<10	14	22.6	7	22.6	7	22.6	0.332#
10-19	23	37.1	8	25.8	15	48.4	
20-29	20	32.3	13	41.9	7	22.6	
30-40	5	8.1	3	9.7	2	6.5	
Residence							
Rural	13	21.0	8	25.8	5	16.1	0.534*
Urban	49	79.0	23	74.2	26	83.9	
Education							
Illiterate	26	41.9	15	48.4	11	35.5	0.525#
Primary	5	8.1	2	6.5	3	9.7	

Middle	10	16.1	4	12.9	6	19.4	
Secondary	9	14.5	5	16.1	4	12.9	
Higher secondary	6	9.7	1	3.2	5	16.1	
Graduate	6	9.7	4	12.9	2	6.5	
Religion							
Hindu	49	79.0	22	71.0	27	87.1	0.211*
Muslim	13	21.0	9	29.0	4	12.9	
Dietary habit							
Mix diet	19	30.6	11	35.5	8	25.8	0.582*
Vegetarian	43	69.4	20	64.5	23	74.2	
Risk factors							
Absent	53	85.5	26	83.9	27	87.1	1.000*
Present	9	14.5	5	16.1	4	12.9	
Fracture							
Absent	49	79.0	25	80.6	24	77.4	1.000*
Present	13	21.0	6	19.4	7	22.6	
Hysterectomy							
Done	6	9.7	2	6.5	4	12.9	0.671*
Not done	56	90.3	29	93.5	27	87.1	

[#] Chi-square test * Fisher Exact Test

Table 2 : Intra group comparison of T score

T Score	Group	Baseline	6 months	12 months	'p' value*
Spine	**Control (N=31)**	-3.16 ± 1.04	-3.16 ± 1.09	-3.19 ± 1.1	0.837
	Denosumab (N=31)	-2.78 ± 0.94	-2.49 ± 0.94	-2.22 ± 0.92	<0.001
Hip	**Control (N=31)**	-2.30 ± 10	-2.38 ± 0.97	-2.41 ± 0.98	0.096
	Denosumab (N=31)	-2.43 ± 1.19	-2.05 ± 1.16	-1.61 ± 1.09	<0.001
Radius	**Control (N=31)**	-3.97 ± 1.4	-3.97 ± 1.30	-4.00 ± 1.33	0.822
	Denosumab (N=31)	-3.41 ± 1.36	-3.14 ± 1.38	-2.83 ± 1.27	<0.001

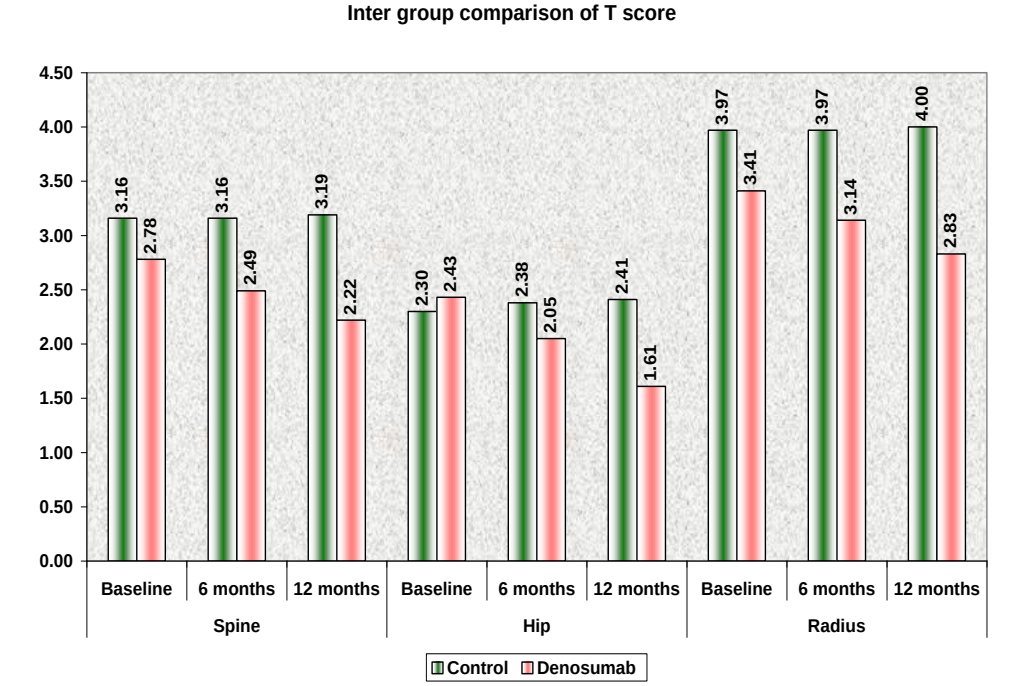
*Repeated Measure AnOVa test

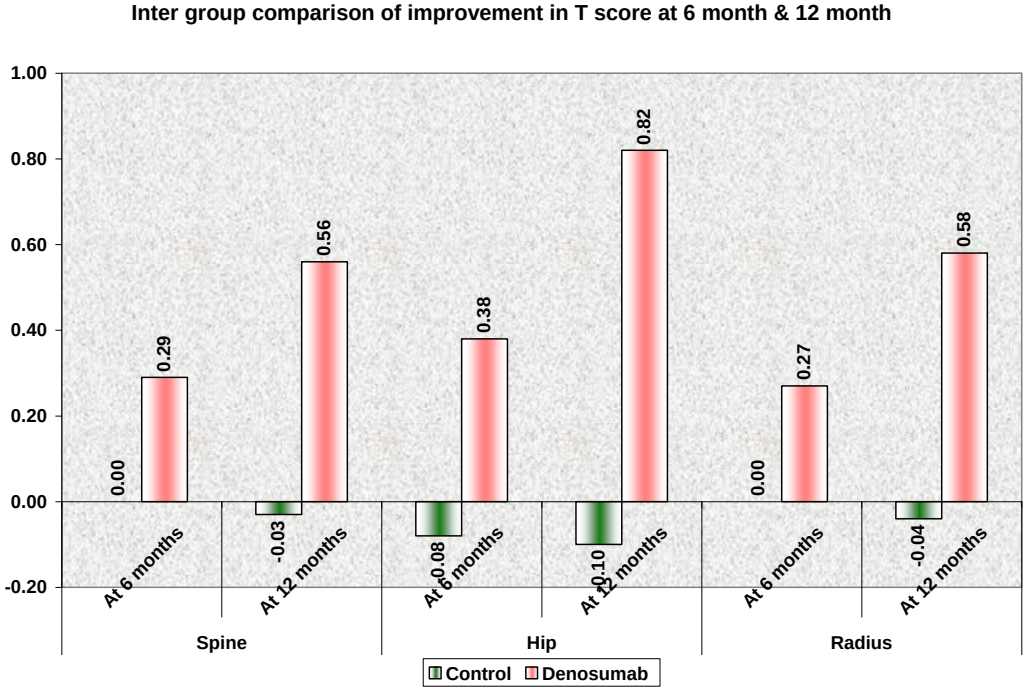
Table 3 : Inter group comparison of T score

T Score	Time interval	Control (N=31)	Denosumab (N=31)	'p' value*
Spine	**Baseline**	-3.16 ± 1.04	-2.78 ± 0.94	0.136
	6 months	-3.16 ± 1.09	-2.49 ± 0.94	0.012
	12 months	-3.19 ± 1.1	-2.22 ± 0.92	<0.001
	Change in 6 months	0.00 ± 0.32	0.29 ± 0.17	<0.001
	Change in 12 months	-0.03 ± 0.41	0.56 ± 0.24	<0.001
Hip	**Baseline**	-2.30 ± 1	-2.43 ± 1.19	0.643
	6 months	-2.38 ± 0.97	-2.05 ± 1.16	0.229
	12 months	-2.41 ± 0.98	-1.61 ± 1.09	0.004
	Change in 6 months	-0.08 ± 0.22	0.38 ± 0.23	<0.001

	Change in 12 months	-0.10 ± 0.36	0.82 ± 0.35	<0.001
Radius	**Baseline**	-3.97 ± 1.4	-3.41 ± 1.36	0.115
	6 months	-3.97 ± 1.3	-3.14 ± 1.38	0.018
	12 months	-4.00 ± 1.33	-2.83 ± 1.27	<0.001
	Change in 6 months	0.00 ± 0.37	0.27 ± 0.25	0.001
	Change in 12 months	-0.04 ± 0.43	0.58 ± 0.34	<0.001

*Unpaired 't' test





Discussion:
Present study found significant improvement in t-score at all 3 sites after 12 months treatment duration with denosumab which is in corroboration with the findings of the study done by Henry G Bone et al, Shailesh Pitale et al, Sugimto et al who also found denosumab as effective treatment of osteoporosis in their studies.

In our study after 12 months treatment duration, t-score was found at all 3 sites significantly more than control group which is similar to the study of Henry G Bone et al[6] who also found that denosumab increases BMD at all 3 sites i.e. lumbar spine, hip and radius in his multicentre, randomized, double-blind, placebo controlled trial in North America. Similarly, Shailesh Pitale et al[7] conducted a double blind, multcentre, randomized controlled trial on 250 Indian postmenopausal women and concluded that treatment with denosumab showed a significant treatment difference compared with placebo after 6 months treatment and these findings are comparable with our study. Sugimoto et al[8] conducted a 2 year randomized, placebo controlled, double blinded study and a 1 year open label extension phase study in 810 Japanese postmenopausal women and men and observed that after 36 months of treatment in the long term group increases BMD significantly at lumbar spine, hip and distal radius compared to those who took placebo for first 24 months. Henry G Bone et al[9] conducted a 2 year randomized double blind placebo controlled trial in North America on 332 postmenopausal women who received denosumab or placebo and they concluded that denosumab significantly increases BMD at lumbar spine, hip and distal radius compared with placebo which is comparable with our findings.

Our study reaffirms that denosumab is helpful in preventing postmenopausal osteoporosis as compared to the standard treatment.
Treatment with denosumab is safe and well tolerated. No adverse reaction was seen in denosumab group during this 1 year of study.

CONCLUSIONS:
One year treatment with denosumab(60 mg every 6 month) is found to be effective in preventing postmenopausal osteoporosis. It increases BMD at hip, spine and radius more than the standard therapy. However, the improvement in t-score after treatment with denosumab at 6 & 12 months was more at hip joint than at spine and radius. Denosumab is a very safe and well tolerated drug which may also be useful in patients with osteoporosis due to other causes such as multiple sclerosis, poliomyelitis and other neurological conditions.

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