Effect of Subcutaneous Administration of Teriparatide in Postmenopausal Osteoporosis

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Abstract— *Postmenopausal osteoporosis is a serious health problem in Indian women as it increases chances of both vertebral and non-vertebral fractures. Currently standard treatment guidelines do not offer any effective prevention of osteoporosis. Teriparatide, in various international studies has been found as an effective treatment option for prevention of postmenopausal osteoporosis. However, there is very limited of data of Indian postmenopausal women. Therefore, present study is an attempt to observe the treatment effect of teriparatide for prevention of postmenopausal osteoporosis.*

Objective: *To observe the treatment effect of teriparatide in patients suffering from postmenopausal osteoporosis in terms of bone mineral density.*

Methods: *This randomized control study was done in 62 randomly selected patients with postmenopausal osteoporosis at SMS Hospital, Jaipur. After administering teriparatide (20 mcg daily), 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 teriparatide group (0.74±1.43, P=0.007) than in control group (0±0.32, P=0.007) and at the end of 12 months also, lumbar spine BMD increased more in teriparatide group (0.8±0.43) than in control group (-0.03±0.41). Similarly, at 6 months, total hip BMD increased more in teriparatide group (0.36±0.45, P<0.001) than in control group (-0.08±0.22, P<0.001) and at the end of 12 months, total hip BMD increased more in teriparatide (0.59±0.45) than in control group (-0.1±0.36).). At 6 months, distal radius BMD increased more in teriparatide group (0.44±0.74, P=0.004) compared to control group (0.00±0.37, P=0.004) and at 12 months, distal radius BMD increased more in teriparatide group (0.77±0.68) compared to control group (-0.04±0.43).*

Conclusions: *Teriparatide is an effective agent to treat postmenopausal osteoporosis and it is more effective at lumbar spine than at hip and radius. To conclude further treatment is needed as sequential therapy because on stopping treatment BMD again start receding over the period.*

Keywords— Teriparatide, Postmenopausal women, Bone mineral density, Osteoporosis.

I. 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] In postmenopausal osteoporosis, cessation of oestrogen secretion 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

growing day by day.[3] BMD in Indian population is comparatively lower than those in Caucasian women[4,5] and fractures are reported to occur 10-12 years earlier than the western population.[6] 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. Currently standard treatment guidelines do not offer any effective prevention of osteoporosis. Teriparatide is approved by FDA for treatment of postmenopausal osteoporosis and the dose is 20 mcg subcutaneously once daily.[2] It is an exogenous PTH analogue which stimulates interstitial growth factor -1 (IGF-1) and collagen production and appears to increase osteoblast number by stimulating replication.[1] Thus it truely increase the bone mass and restores bone microarchitecture.[7,8] Various international studies has shown that teriparatide is an effective treatment option for prevention of postmenopausal osteoporosis.

II. OBJECTIVES

To observe the treatment effect of teriparatide 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.

III. 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 teriparatide 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 routine investigations and specific investigations like DEXA scan, vitamin D3 was done. In intervention group injection teriparatide 20 mcg subcutaneously once daily was given for 1 year 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.

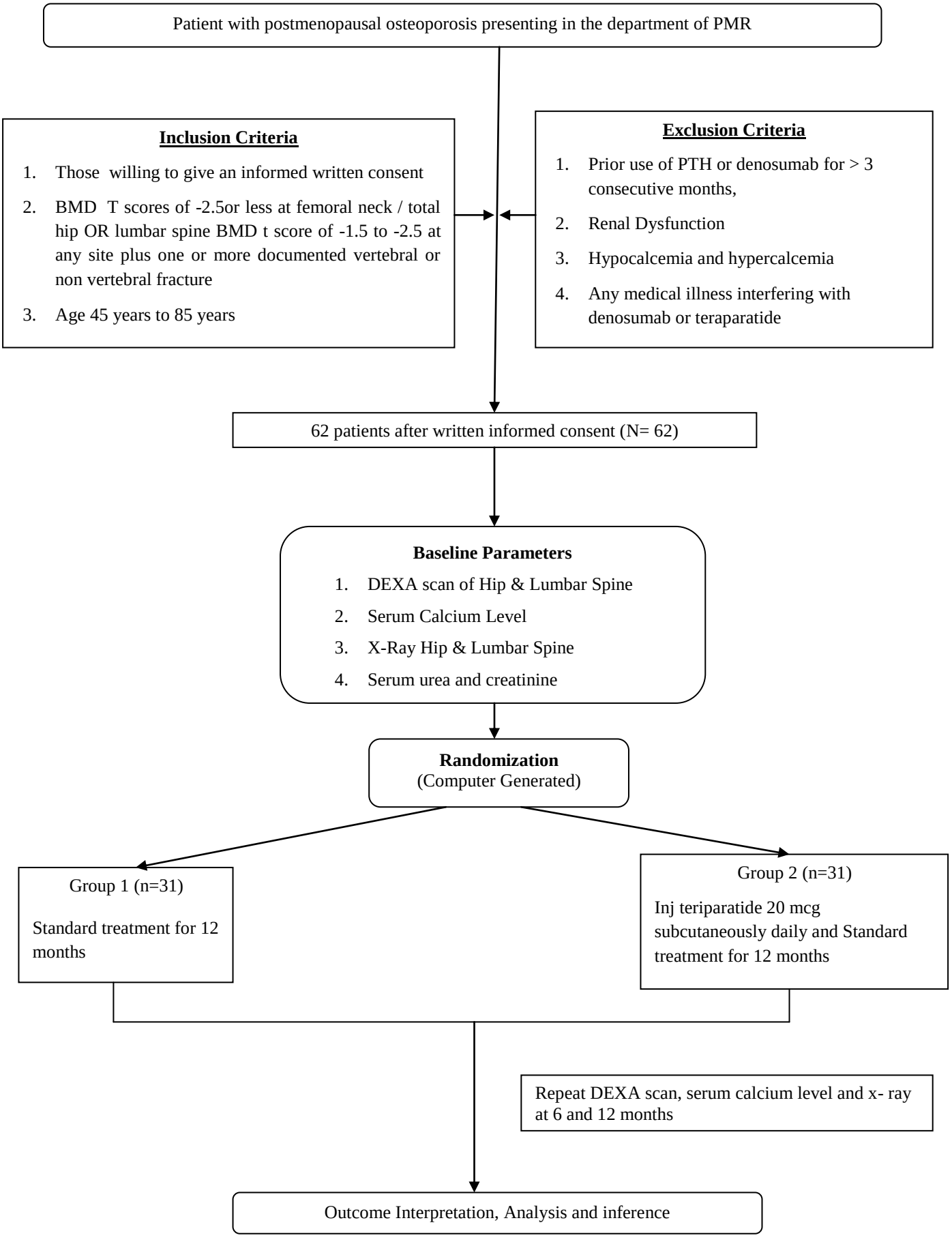
IV. DATA ANALYSIS

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.

Flow Chart


Patient with postmenopausal osteoporosis presenting in the department of PMR
Inclusion Criteria
1. Those willing to give an informed written consent
2. BMD T scores 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
3. Age 45 years to 85 years
Exclusion Criteria
1. Prior use of PTH or denosumab for > 3 consecutive months,
2. Renal Dysfunction
3. Hypocalcemia and hypercalcemia
4. Any medical illness interfering with denosumab or teraparatide
62 patients after written informed consent (N= 62)
Baseline Parameters
1. DEXA scan of Hip & Lumbar Spine
2. Serum Calcium Level
3. X-Ray Hip & Lumbar Spine
4. Serum urea and creatinine
Randomization
(Computer Generated)
Group 1 (n=31)
Standard treatment for 12 months
Group 2 (n=31)
Inj teriparatide 20 mcg subcutaneously daily and Standard treatment for 12 months
Repeat DEXA scan, serum calcium level and x- ray at 6 and 12 months
Outcome Interpretation, Analysis and inference

V. 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 62.44±9.71 years and 25.33±4.33 kg/m^2.

When patients were randomized into teriparatide and control group, mean age and BMI of patients of teriparatide group was 62.16±9.51 years & 26.17±4.58 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).

TABLE 1
GENERAL CHARACTERISTICS OF STUDY PARTICIPANTS

	Total (N=62)		Control (N=31)		Teriparatide (N=31)		'p' value*
Age group (Years)	**No.**	**%**	**No.**	**%**	**No.**	**%**	
<50	7	11.3	4	12.9	3	9.7	0.813#
50-59	18	29	9	29.0	9	29	
60-69	22	35.5	9	29.0	13	41.9	
≥70	15	24.2	9	29.0	6	19.4	
PMP period							
<10	15	24.2	7	22.6	8	25.8	1.000#
10-19	14	22.6	8	25.8	6	19.4	
20-29	26	42	13	41.9	13	41.9	
30-40	7	11.2	3	9.7	4	12.9	
Residence							
Rural	11	17.7	8	25.8	3	9.7	0.184*
Urban	51	82.3	23	74.2	28	90.3	
Education							
Illiterate	25	40.3	15	48.4	10	32.3	0.741#
Primary	5	8	2	6.5	3	9.7	
Middle	7	11.3	4	12.9	3	9.7	
Secondary	12	19.4	5	16.1	7	22.6	
Higher secondary	5	8	1	3.2	4	12.9	
Graduate	8	13	4	12.9	4	12.9	
Religion							
Hindu	49	79.0	22	71.0	27	87.1	0.212*
Muslim	13	21.0	9	29.0	4	12.9	
Dietary habit							
Mix diet	17	27.4	11	35.5	6	19.4	0.255*
Vegetarian	45	72.6	20	64.5	25	80.6	
Risk factors							
Absent	48	77.4	26	83.9	22	71	0.362*
Present	14	22.6	5	16.1	9	29	
Fracture							
Absent	51	82.3	25	80.6	26	83.9	1.000*
Present	11	17.7	6	19.4	5	16.1	
Hysterectomy							
Done	8	13	2	6.5	6	19.4	0.256*
Not done	54	87	29	93.5	25	80.6	

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 teriparatide 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).

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
	Teriparatide (N=31)	-2.83 ± 1.08	-2.16 ± 1.7	-2.1 ± 0.99	0.001
Hip	**Control (N=31)**	-2.30 ± 10	-2.38 ± 0.97	-2.41 ± 0.98	0.096
	Teriparatide (N=31)	-2.38 ± 0.78	-2.09 ± 0.72	-1.85 ± 0.72	<0.001
Radius	**Control (N=31)**	-3.97 ± 1.4	-3.97 ± 1.30	-4.00 ± 1.33	0.822
	Teriparatide (N=31)	-3.84 ± 1.5	-3.51 ± 1.43	-3.17 ± 1.36	<0.001

Repeated Measure AnOVa test

Mean t-score of spine in teriparatide group was -2.83, -2.16 & -2.1 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 teriparatide 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 teriparatide group was found statistically significantly higher at 12 months than control group, but not at baseline and 6 months (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 teriparatide 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 3
INTER GROUP COMPARISON OF T SCORE

T Score	Time interval	Control (N=31)	Teriparatide(N=31)	'p' value*
Spine	**Baseline**	-3.16 ± 1.04	-2.83 ± 1.08	0.225
	6 months	-3.16 ± 1.09	-2.16 ± 1.7	0.008
	12 months	-3.19 ± 1.1	-2.1 ± 0.99	<0.001
	Change in 6 months	0.00 ± 0.32	0.74± 1.43	0.007
	Change in 12 months	-0.03 ± 0.41	0.8 ± 0.43	<0.001
Hip	**Baseline**	-2.30 ± 1	-2.38 ± 0.78	0.727
	6 months	-2.38 ± 0.97	-2.09 ± 0.72	0.186
	12 months	-2.41 ± 0.98	-1.85 ± 0.72	0.013
	Change in 6 months	-0.08 ± 0.22	0.36 ± 0.45	<0.001
	Change in 12 months	-0.10 ± 0.36	0.59 ± 0.45	<0.001
Radius	**Baseline**	-3.97 ± 1.4	-3.84 ± 1.5	0.726
	6 months	-3.97 ± 1.3	-3.51 ± 1.43	0.190
	12 months	-4.00 ± 1.33	-3.17 ± 1.36	<0.018
	Change in 6 months	0.00 ± 0.37	0.44 ± 0.74	0.004
	Change in 12 months	-0.04 ± 0.43	0.77 ± 0.68	<0.001

Unpaired 't' test

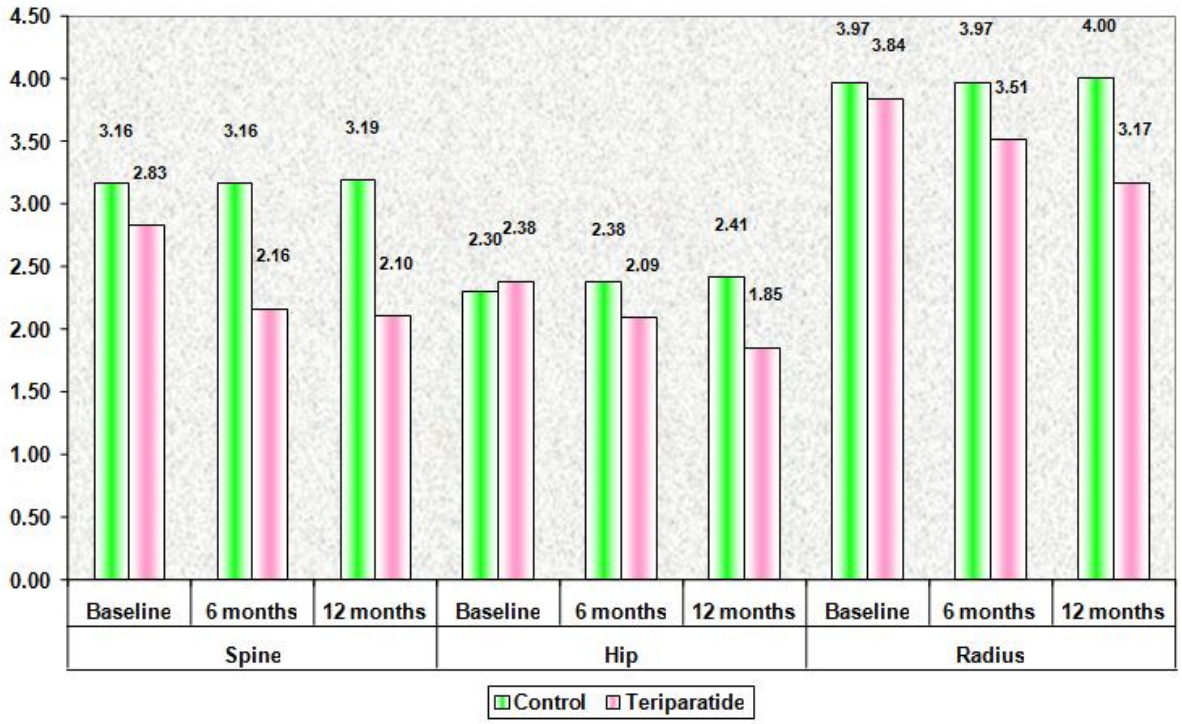


FIGURE 1: Inter group comparison of T score

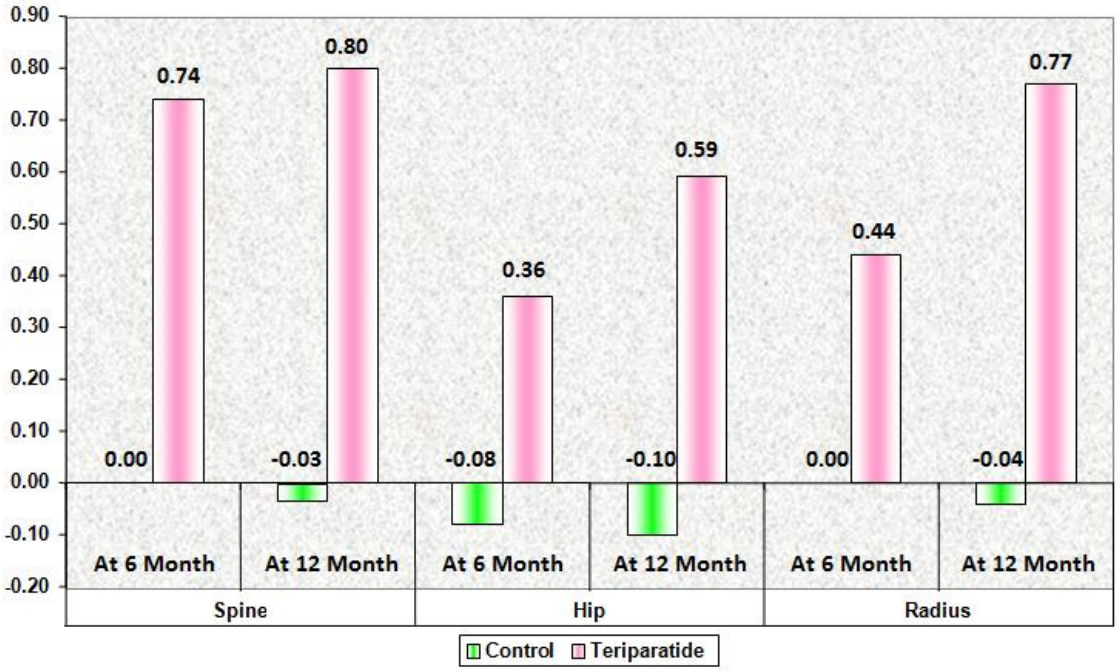


FIGURE 2: Inter group comparison of improvement in T score at 6 month & 12 month

VI. DISCUSSION

Present study found significant improvement in t-score at all 3 sites after 12 months treatment duration with teriparatide which is in conformity with the findings of the study done by Miyauchi et al, BK Sethi et al, Satoshi Soen et al who also found teriparatide as effective treatment of osteoporosis in their studies.

In our study after 12 months treatment duration with teriparatide, t-score was found at all 3 sites significantly more than control group which is similar to the study of Miyauchi et al[9] who also found that teriparatide increases BMD at spine and hip in his multicentre, randomized, placebo-controlled study in Japan. Similarly, BK Sethi et al[10] conducted a randomized,

prospective, multicentre, open-label controlled study in 82 postmenopausal women and concluded that treatment with teriparatide for 6 months significantly increases lumbar spine BMD compared to control group and this finding is comparable with our study. Satoshi Soen et al[11] conducted a multicentre, prospective study on 1996 patients in Japan and observed that after 12 and 24 months, treatment with teriparatide increases BMD at lumbar spine and total hip which is comparable with our findings.

Our study reiterates that teriparatide prevents postmenopausal osteoporosis as compared to standard treatment.

Treatment with teriparatide is safe and well tolerated. One subject developed localized skin rashes at injection sites which was self-limiting , no other serious side effect was noted during this 12 months of follow up period.

VII. CONCLUSION

One year treatment with teriparatide (20 mcg daily) is found to be effective in preventing postmenopausal osteoporosis. It increases BMD at spine, hip and radius more than the standard therapy. However, the improvement in t-score after 1 year treatment with teriparatide at 6 and 12 months was more at spine than at hip and radius. Teriparatide is a safe and well tolerated with minimal side effects 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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