Outcome of bisphosphonate, vitamin D and calcium therapy in patients with established osteoporosis based on FRAX model

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Abstract
Introduction: WHO defined Osteoporosis as a bone mineral density (BMD) of 2.5 SD or more below the mean peak bone mass (average of young, healthy adults) as measured by dual-energy X-ray absorptiometry. FRAX is a computer-based algorithm developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases and first released in 2008. The output of FRAX is the 10-year probability of a major osteoporotic fracture and the 10-year probability of hip fracture.
Objective: To assess the outcome of combined bisphosphonate, vitamin D and calcium therapy in patients with established osteoporosis at the end of 15 months, to assess the relationship between vit D, Calcium and osteoporosis with reference to existing FRAX model and to analyze whether any correlation exists between serum Vitamin D levels and BMD as established by DEXA Scan.
Materials and Methods: A prospective observational study was performed in 128 patients who underwent screening with Vitamin D levels and DEXA scan to confirm osteoporosis. DEXA scan was employed primarily to establish a case as osteoporosis according to the definition. These patients were started on treatment with combined Bisphosphonates standard dosage of alendronate 70 mgs once per week with standard instructions for 15 months, Vitamin D was administered to patients with established hypovitaminosis as standard therapy with oral sachet of 60,000 I.U administered with milk for 8 weeks. Calcium supplements were given as calcium carbonate 1G per day for 15 months. The final assessment was done by the end of 15 months by analyzing the results of BMD and Vitamin D levels to look for any improvement.
Results: In our study of 128 patients we found that, there was statistically significant improvement in mean ± SD Vit D and FRAX hip score at end of study while comparing with pretreatment scores. There was a strong positive correlation between FRAX score hip and FRAX score osteoporosis.
Conclusion: The combination of vitamin D3, bisphosphonate and calcium improves bone mineral density and reduces the risk of hip and other osteoporotic fractures at the end of 15 months based on FRAX model.

Keywords: Osteoporosis, Bone mineral density, Z score, FRAX.

Introduction
WHO defined Osteoporosis as a bone mineral density (BMD) of 2.5 SD or more below the mean peak bone mass (average of young, healthy adults) as measured by dual-energy X-ray absorptiometry.[1] Osteoporosis is also defined as the reduction in bone per unit volume, osseous trabeculae which normally maintain a constant organic and mineral structure. As a result of this thinning, the spaces between trabeculae become larger, and compact bone is transformed into spongy bone with more open texture. The net amount of bone tissue is decreased. Despite thinning of bone trabeculae and loss of fine trabeculation, histological evidence shows a normal degree of calcification but with marked reduction in the number of cells. These anatomical changes are accompanied by normal levels of serum calcium, serum phosphorus and serum alkaline phosphatase.[2]

Every second woman and every third man over the age of 50 will eventually suffer from an osteoporosis-related fracture. The lifetime risk for an osteoporotic fracture of the hip, spine or wrist has been reported to be 40% for Caucasian women in Europe.[3] The risk for a hip fracture is between 11% and 18% in women, which is equal to the combined risk for breast, uterine, and ovarian cancers.[4,5] Fractures are between two and three times more prevalent than those in the hip but only one third are ever diagnosed.[6] In the US alone, 1.5 million fractures, including 250 000 of the hip, 250 000 of the distal radius and 700 000 of the vertebrae occur each year secondary to osteoporosis. In the UK over 300 000 osteoporotic fractures are sustained each year.[7-11]

FRAX is a computer-based algorithm developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases and first released in 2008. The algorithm, intended for primary care, calculates fracture probability from easily obtained clinical risk factors (CRFs) in men and women. The output of FRAX is the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture.[12,13]

Objectives
Primary objective
To assess the outcome of combined bisphosphonate, vitamin D and calcium therapy in patients with established osteoporosis at the end of 15 months.

Secondary objectives
1. To assess the relationship between vit D, Calcium and osteoporosis with reference to existing FRAX model.
2. To analyze whether any correlation exists between serum Vitamin D levels and BMD as established by DEXA Scan.

Materials and Methods

With a level IV evidence, a prospective observational study was performed from August 2016 to July 2018 in the department of Orthopaedics, JJM Medical College, Davangere. The study was conducted to analyze the effect of combined bisphosphonate, vitamin D and calcium therapy in patients with established osteoporosis confirmed by DEXA scan in urban population at the end of 15 months based on FRAX model. This study was conducted with intent to treat.

The males over 60 years of age with established osteoporosis (T score <-2.5) and postmenopausal females over the age of 50 years with established osteoporosis (T score <-2.5) were included in the study. The major medical illness such as renal disorders, liver disorders, hyperparathyroidism, hyperthyroidism, recent history of cancer, metabolic bone disease within the past year, recent use of drugs known to affect the bone (thiazides, antiepileptics, glucocorticoids, wafarin), allergy to bisphosphonates, previous history of fractures, smoker and alcoholic, patients suffering from secondary osteoporosis were excluded from the study.

The cases for this study were recruited by convenient sampling technique. A total of 145 patients, who satisfy the inclusion and exclusion criteria, were enrolled in the study. Out of 145 patients, 17 patients were lost for follow up. Hence, 128 patients were followed up for a period of 15 months and subjected for statistical analysis. Appropriate statistics tool was employed to understand descriptive, demographic and analytical measures. Parametric variables are calculated with T test and paired students t test and 2 tailed student t test. Intra-observer variations in interpreting the DEXA scan will be minimized by single observer and interpreter. Statistical analyses was done utilizing SPSS Version 24.0 software.

Results

Out of 145 patients included in our study about 17 patients were lost in the follow up. Hence based on strict inclusion and exclusion criterion remaining 128 patients were followed up to 15 months (study time duration). The patients included in the study underwent screening with Vitamin D levels and DEXA scan to confirm osteoporosis. DEXA scan was employed primarily to establish a case as osteoporosis according to the definition. These patients were started on treatment with combined Bisphosphonates standard dosage of alendronate 70 mgs once per week with standard instructions for 15 months, Vitamin D was administered to patients with established hypovitaminosis as standard therapy with oral sachet of 60,000 I.U administered with milk for 8 wks. Calcium supplements were given as calcium carbonate 1G per day for 15 months.

Final assessment was done by the end of 15 months by analyzing the results of BMD and Vitamin D levels to look for any improvement. This study did not consider subjective assessments since osteoporosis is a silent epidemic and in pretreatment status most of the patients were asymptomatic. During this study none of the patients who were followed up till the completion period demonstrate any adverse events to administered drugs.

In our study, 121 cases were female and 7 cases were male. The minimum age was 54 years and maximum was 88 years. The minimum weight was 31 kg and maximum was 90 kg. Among the patients, minimum BMI (Kg/m2) was 14 and the maximum was 41. Among 128 patients, the minimum femoral neck BMD was -5.6 and maximum was -2.5. Of the total 128 patients, 5 patients (3.9%) were on steroids, criteria for a patient to be on steroid is explained under the FRAX description. 12 (9.4%) out of 128 patients were diagnosed to have RA and were on treatment.

The mean Vit D level at baseline was 23.95(9.49) and at the end of the study it was 32.33 (7.26). The average dose of Vit D (calciferol granules) was 60,000 IU, once a week for eight weeks. It is observed that the increase in Vit D level was statistically significant (p<0.001) as shown in Fig. 1.

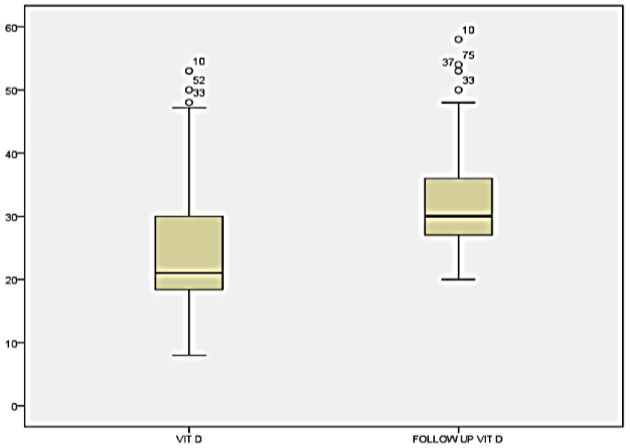

Fig. 1: Box and Whisker plot depicting the mean ± SD Vit D levels at base line and end of the study

We can infer that FRAX score hip at baseline was 6.8 (6.6), at the end of the study it was 4.5 (4.0). It was observed that the change in values of FRAX score hip was statistically significant (p <0.001) as shown in Fig. 2.

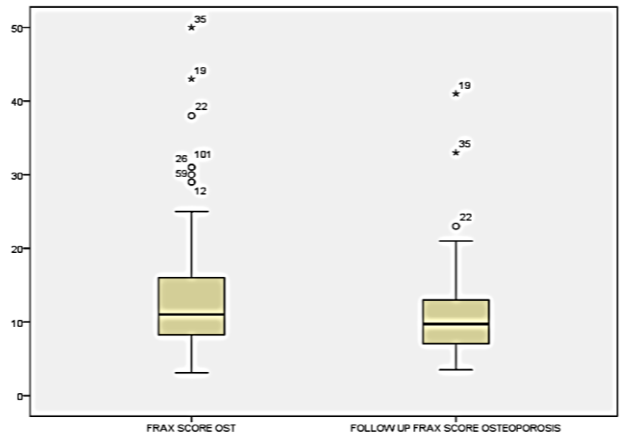

Fig. 2: Box and Whisker plot depicting the mean ± SD FRAX score osteoporosis at base line and end of the study

There was a direct positive correlation between Vit D and Femoral neck BMD (0.415) as shown in Fig. 3.

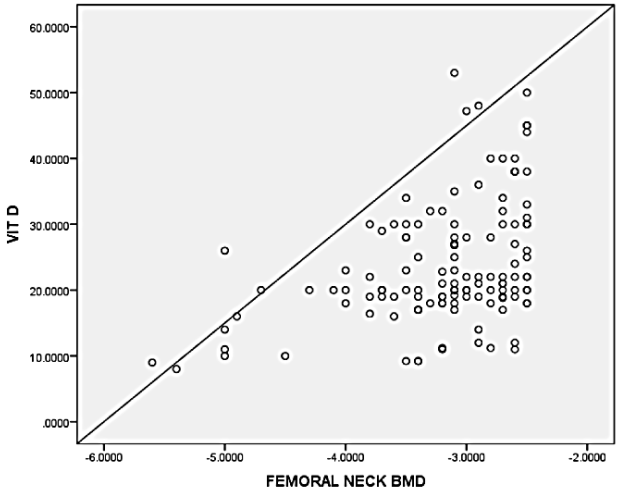

Fig. 3: Scatter plot showing correlation between Vit D and femoral neck BMD

In our study of 128 patients we found that, there was statistically significant improvement in mean ± SD Vit D from 23.95 ± 9.49 to 32.33 ± 7.26 at end of study. The mean ± SD FRAX hip score at the beginning of our study was 6.8 ± 6.6 and at the end of the study it was 4.5 ± 4.0 which was statistically significant. There was statistically significant improvement in the FRAX score osteoporosis from 13.07 ± 7.7 to 10.4 ± 5.2.

Table 1: Correlational studies between FRAX score hip, FRAX score osteoporosis and other variables

Variables		**FRAX score Hip**	**FRAX score Osteoporosis**
FRAX score hip	Pearson Correlation	1	.952**
	Sig. (2-tailed)		.000
	N	128	128
FRAX score osteoporosis	Pearson Correlation	.952**	1
	Sig. (2-tailed)	.000	
	N	128	128
Follow up Vit D	Pearson Correlation	-.172	-.199*
	Sig. (2-tailed)	.052	.024
	N	128	128
Follow up score Hip	FRAX	.928**	.914**
	Sig. (2-tailed)	.000	.000
	N	128	128
Follow up femoral BMD	Femoral Neck	-.874**	-.854**
	Sig. (2-tailed)	.000	.000
	N	128	128
Follow up FRAX score osteoporosis	Pearson Correlation	.860**	.918**
	Sig. (2-tailed)	.000	.000
	N	128	128
Vitamin D	Pearson Correlation	-.439**	-.511**
	Sig. (2-tailed)	.000	.000
	N	128	128
Femoral BMD	Neck	-.885**	-.871**
	Sig. (2-tailed)	.000	.000
	N	128	128
BMI	Pearson Correlation	-.130	-.075
	Sig. (2-tailed)	.144	.402
	N	128	128

From table 1, there was a strong positive correlation between FRAX score hip and FRAX score osteoporosis. It was interesting to observe that there was established positive correlation between follow up FRAX score hip and FRAX score osteoporosis also.

Table 2: Correlational studies between femoral neck BMD, BMI and other variables

Variables		Femoral neck BMD	BMI
FRAX score hip	Pearson Correlation	-.885**	-.130
	Sig. (2-tailed)	.000	.144
	N	128	128
FRAX score osteoporosis	Pearson Correlation	-.871**	-.075
	Sig. (2-tailed)	.000	.402
	N	128	128
Follow up Vit D	Pearson Correlation	.183*	-.122
	Sig. (2-tailed)	.039	.170
	N	128	128
Follow up score Hip	FRAX	-.827**	-.096
	Sig. (2-tailed)	.000	.279
	N	128	128
Follow up femoral BMD	Femoral Neck	.973**	.071
	Sig. (2-tailed)	.000	.425
	N	128	128
Follow up FRAX score osteoporosis	Pearson Correlation	-.767**	-.041
	Sig. (2-tailed)	.000	.643
	N	128	128
Vitamin D	Pearson Correlation	.415**	-.015
	Sig. (2-tailed)	.000	.867
	N	128	128
Femoral BMD	Neck	1	.092
	Sig. (2-tailed)		.301
	N	128	128
BMI	Pearson Correlation	.092	1
	Sig. (2-tailed)	.301	
	N	128	128

From table 2, we can infer that there was a strong inverse relation between femoral neck BMD and FRAX score hip, a strong inverse relation between femoral neck BMD and FRAX score osteoporosis and a strong inverse relation between femoral neck BMD and follow up FRAX score hip and follow up FRAX score osteoporosis.

Discussion

This was prospective observational study conducted to analyze the effect of combined bisphosphonate, vitamin D and calcium therapy in patients with established osteoporosis confirmed by DEXA scan in urban population based on FRAX model at end of 15months. The study was conducted with intent to treat, although various studies are available describing the effect of vitamin D, bisphosphonate and calcium in the treatment of osteoporosis in different populations, very few studies are available on the combined effect of vitamin D, bisphosphonate and calcium and no studies are available on Indian population where FRAX model has been incorporated into the study.

In this study comparing the levels of vitamin D, BMD, FRAX score hip and osteoporosis before and after treatment in the same individual. Paired T test was used in statistics to draw conclusions statistically.

In this study the patients with 60,000 IU of Vitamin D weekly for 8 weeks, the mean ± SD Vit D levels at the beginning were 23.95 ± 9.49 and found that there was statistically significant improvement in serum vitamin D levels at the end of the study 32.33 ± 7.26.

Compared to the study on the effect of Vitamin D3 and Calcium on fracture risk in 65 to 71 year old women: a population based 3 year RCT - The OSTPRE-FPS: Kari Salovaara et al‘, where they found that Vit D and calcium therapy did not produce a statistically significant result on fracture risk reduction on Finnish population.[14] But our study showed statistical significant improvement in Vit D levels and improvement in bone mineral density at end of 15 months which in-turn showed fracture risk reduction in our population.

The mean ± SD FRAX hip score at the beginning of our study was 6.8 ± 6.6 and at the end of the study it was 4.5 ± 4.0 which was statistically significant. There was statistically significant improvement in the FRAX score osteoporosis from 13.07 ± 7.7 to 10.4 ± 5.2. There was a positive

correlation between BMI and BMD which reinforces the fact that BMI can be used as an alternative to BMD in FRAX model where facilities to check BMD are not available.

From the scatter plot between Vit D and BMD we found positive correlation between the two variables.

The significant implications of the findings were the combined use of Vit D, bisphosphonate and calcium in patients with established osteoporosis gave us a statistically significant result in improving the BMD of patients as evaluated by FRAX model.

In this study there was a direct correlation between Vit D and BMD, hence clinically this study will help us in making an informed choice, about the investigations to be requested in clinical practice. Requesting one of the tests would reduce the financial burden on the patient, where if Vit D was low and there is no facility to measure BMD we can draw comparable conclusion with Vit D, however if we measure BMD and not vit D, it would be prudent to still measure Vit D before starting treatment as hypervitaminosis D is a well-documented adverse effect.

Treating the patients with Vit D (60 000 IU) for a period of 8 weeks resulted in significant improvement which will help us in reducing the treatment duration and cost for the patient. Taking into consideration the financial burden of the disease, this study will advocate the importance and cost-effectiveness of treatment for osteoporosis.

Limitations

1. The subjects were studied once in the beginning and at the end of study, although patients were followed up regularly investigations were done only at the end of the study, hence mean index score analysis was not carried out.
2. External validation of the study was not performed
3. A double blind randomized controlled study would give us level 1 evidence on the results obtained.
4. The sample size was low and male subjects were very limited and results were not described independently for male and female.

Future Research recommendations

1. A double blind RCT, with respect to effect vitamin D, bisphosphonate and calcium on BMD, based on FRAX model would give level 1 evidence which can be incorporated into practice.[15]
2. The effect of Teriparatide and combination of teriparatide, calcium and vitamin D on BMD would throw more light on the efficacy of current treatment options.
3. A randomized controlled trial to find the relationship between Vit D and BMD, which will help us in being cost effective during investigations.

Conclusion

Bone mineral density plays an important role in preventing osteoporotic fracture in older patients. FRAX algorithm, gives us 10 year probability of hip fracture and other osteoporotic fracture taking into consideration bone mineral density and the risk factors. The combination of Vit D, bisphosphonate and calcium was able to bring about statistically significant improvement in bone mineral density of patients at the end of 15 months; they were also able to reduce the probability of hip fracture and osteoporotic fracture at the end of 15 months based on FRAX model.

As a corollary, there was positive correlation between Vit D and BMD & between BMI and BMD. To conclude, Vit D, bisphosphonate and calcium improves bone mineral density and reduces the risk of hip and other osteoporotic fractures at the end of 15 months based on FRAX model.

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Nil.

Conflict of interest

Nil.

Acknowledgements

Nil.

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