Comparative study of Vitamin D and Parathyroid Hormone Status among Fragility Hip Fracture Cases and Elderly Control Subjects in Rajasthan, India

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ABSTRACT

Introduction: Vitamin D deficiency and secondary hyperparathyroidism play central role in pathogenesis of fragility hip fractures among geriatric population. Osteoporosis, osteomalacia, deranged renal profile and poor muscle function lead to brittle bones and frequent falls which together are important in causation of hip fractures. Aim of the study was to characterize and quantify Vitamin D and Parathyroid hormone levels among the elderly patients with fragility hip fractures and apparently healthy controls among patients of Rajasthan state, India.

Material and Methods: 64 elderly (age>60 years) subjects suffering from non-traumatic hip fractures and 64 healthy control subjects included in study and their venous blood samples were analyzed for vitamin D, PTH, alkaline phosphatase and serum calcium levels.

Results: A high prevalence of vitamin D deficiency (90.65%) was found in case group compared to 68.75% among controls. Mean serum 25(OH)D was 12.47±4.52 ng/ml in hip fracture group which was significantly lower than control group levels i.e. 17.57±5.21 ng/dl. Serum PTH (mean±SD) was 62.74±21.05 pg/ml among hip fracture case group which was significantly higher than of control group (44.43±16.07) pg/ml. Serum vitamin D levels correlated negatively with serum PTH levels.

Conclusion: Hypovitaminosis D is prevalent not only among sufferers of fragility fractures but also in general elderly population which might be due to their housebound habitat and poor nutritional supply. In Indian perspective its not possible to screen whole population for vitamin D deficiency, hence routine supplementation of vitamin D for general elderly population is recommended to combat the problem.

Keywords: Fragility fractures, Hip fractures, Osteoporosis, secondary hyperparathyroidism, vitamin D deficiency.

INTRODUCTION

Fragility fractures are major contributor to the burden of public health problem globally. Among these the most common are osteoporotic spine fractures but hip fractures are the most severe ones in terms of morbidity and mortality.[1] Vitamin D deficiency causes osteomalacia in adults particularly among geriatric group due to low sunshine exposure and low dietary intake.[1,2] Osteomalacia and low calcium nutrition together causes stimulation of parathyroid glands and resultant secondary hyperparathyroidism leading to cortical bone loss which is a major pathway in causation of fragility hip fractures.[1]

Vitamin D is synthesized in skin from its precursor 7-dehydrocholesterol under the influence of solar UV-B radiation (290-315nm).[3] Some foods also contain vitamin D in low amount e.g. fatty fishes, dairy products, egg. Vitamin D deficiency among geriatric population is caused by low sunshine exposure and poor nutrition. Previous studies confirm that a low vitamin D level is associated with increased risk of osteoporotic hip fractures.[4,5] Studies also revealed that prophylactic supplementation of vitamin D causes significant rise in serum vitamin D levels and reduced serum PTH and alkaline phosphatase levels which were previously found to be increased.[1,6]

Documenting the prevalence of vitamin D deficiency and secondary hyperparathyroidism is of vital importance as a first step in rising awareness among orthopaedic surgeon and further determining a screening and treatment strategy in elderly orthopaedic patients. Reports documenting the incidences of hypovitaminosis D and consequent secondary hyperparathyroidism in elderly orthopaedic patients compared to apparently healthy population are sparse in Indian literature. The purpose of this study is to characterize and quantify Vitamin D and Parathyroid hormone levels among the elderly patients with fragility hip fractures and apparently healthy controls among patients of Rajasthan state, India.

MATERIAL AND METHODS

Study subjects: The present study was conducted at Department of Orthopaedics, SMS Medical college Jaipur Rajasthan India. 64 cases of radiographically proven hip fractures resulting from trivial trauma which comprised of 40 males and 24 female elderly (age>60 years) subjects fulfilling inclusion criteria included in the study and termed case group.

Another study group consists of 64 apparently healthy elderly subjects who attended outpatient department of hospital for non-orthopaedic problems included in study and termed control group.

Inclusion criteria

- Patients giving informed consent to take part in study.
- Patients having hip fracture after trivial trauma with age 60 years or more.

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- Elderly healthy individuals not having hip fracture with age 60 years or more.

Exclusion Criteria

- Polytraumatized patients.
- Patients with history of significant traumatic event.
- Patients with previous history of non-traumatic fracture.
- Patients with age less than 60 years.
- Patients with history of intake of drugs that can affect bone mineral metabolism like systemic steroids, anti-osteoporotic medications, anti-tubercular drugs, anti-epileptic drugs, bisphosphonates, levothyroxine, teriparatide, warfarin, OCPs
- Patients with history of major surgery, prolonged hospitalization or major medical illness within the past one year.
- Patients suffering from major systemic illness like diabetes mellitus, malignancy, hepatic, renal, connective tissue or dermatological, malabsorption, endocrinal disorder.
- Persons taking vitamin or mineral supplementations.
- Patients with a history of hysterectomy/hormone replacement therapy

Ethical Clearance: All good clinical practice (GCP) guidelines were followed. The ethical Review Board approved the study and informed consent was obtained from all patients and control subjects.

Clinical history and examination: A detailed questionnaire regarding name, age, sex, residential address, h/o injury regarding date and mechanism of injury, h/o smoking and alcoholism, occupational status were recorded. Patient's general condition and vitals were assessed and noted. History of past/present medical or surgical illness was noted with detailed note on past/present medical/surgical treatment patient received.

Work Up: From each study subject 10ml of blood sample was drawn without venostasis. The samples were placed in ice boxes. Whole blood was transported under chilled condition to the laboratory in batches. In laboratory serum was separated after centrifugation at 3000 RPM for 15 min at 4°C. After centrifugation the serum was stored in the laboratory freezer at minus 20°C, until further analysis. The venous blood samples for PTH analysis were collected in EDTA plasma collection tubes. Serum 25(OH)D concentrations were estimated by using Enzyme Immunoassay (EIA). Other serum markers measured included total calcium, intact parathyroid hormone (i-PTH) and alkaline phosphatase.

STATISTICAL ANALYSIS

As shown in table-1**,** Statistical analysis was performed with the SPSS, trial version 20 for Windows statistical software package (SPSS inc., Chicago, il, USA) and primer. The Categorical data were presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was expressed as mean ± SD (Standard Deviation). Differences among the groups were analyzed using the student T Test for parametric data and Mann-Whitney *U* test for the non-parametric. The test of normality was done by Kolmogorov-Smirnov test and skewness and kurtosis statistics According to this, Age and S calcium is non-parametric data. Relationships between variables in the patient group were assessed by using Pearson's correlation coefficient. Significance level was set at $P < 0.05$.

If the sample size is larger than 50, we use the Kolmogorov-Smirnov test. If the sample size were 50 or less, we use the Shapiro-Wilk statistic instead. The test of normality was done by Kolmogorov-Smirnov test. The null hypothesis for the test of normality states that the actual distribution of the variable is equal to the expected distribution, i.e., the variable is normally distributed. Since the probability associated with the test of normality (0.001) is less than the level of significance (0.01), we reject the null hypothesis.

For staging vitamin D deficiency Paul Lips developed a staging system, which takes into account the 3 different parameters-serum 25(OH)D levels, serum PTH levels and bone histology.[1] We stratified the data on the basis of the same.

RESULTS

As shown in table-2, both the groups were comparable regarding age distribution. Mean±SD age of the case group and controls groups are 69.63± 6.90 (range 60 to 85 years) and 67.47±5.768 years (range 60 to 82 years). On application of Chi-square test no significant difference was found between study groups (*P value=0.064*). Most of the subjects belong to 65-69 year of age group in case group (34.38%), while maximum percentage of subjects in control group (32.81%) lied in 60-64 years age slot, a little higher than 65-69 years slot (31.25%).

As depicted in table-3, we stratified the data on vitamin D according to defined by Paul Lips.[1] The percentage of patients and control subjects with hypovitaminosis D according to different cut points were:

GROUP		Kolmogorov-Smirnov[b]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Age	Case	.150	64	.001	.928	64	.001
	Control	.197	64	.000	.898	64	.000
Vit D(ng/ml)	Case	.090	64	.200*	.969	64	.105
	Control	.068	64	.200*	.990	64	.903
PTH(pg/ml)	Case	.100	64	.189	.960	64	.037
	Control	.071	64	.200*	.979	64	.354
S. Calcium(mg/dl)	Case	.136	64	.005	.927	64	.001
	Control	.184	64	.000	.931	64	.002
S. Alkaline Phosphatase(IU/Lt)	Case	.100	64	.188	.958	64	.030
	Control	.075	64	.200*	.983	64	.500
*This is a lower bound of the true significance.							

Table-1: Assessment of variables for Tests of Normality

1. **>30ng/ml** normal or sufficient levels were observed in 0% of the cases while 1.56% controls had the same level of vitamin D.
2. **20 to 30 ng/ml** Vitamin D insufficient or borderline levels were observed in 9.38 % cases and 29.69 % controls.
3. **10 to 20 ng/ml** mild deficiency of vitamin D observed in 57.81% of cases and 59.38% of control subjects;
4. **5 to 10 ng/ml** moderately deficient levels of vitamin D were found in 28.13% cases and 9.38% control subjects.

58 out of the total 64 hip fracture cases i.e. a total of 90.65% cases were found to be vitamin D deficient (<20ng/ml) and rest 6 cases were in vitamin D insufficiency range (>30ng/ml). No hip fracture case found to have sufficient serum vitamin D level. 44 out of the total 64 control group (68.75%) were found to be vitamin D deficient, while 19 control subjects (29.69%) were having insufficient levels, and 1 control subject had sufficient serum vitamin D levels. The percentage of patients with severe hypovitaminosis D **(<5 ng/ml)** among cases was 4.69 %, compared to 0% in the control group.

As shown in table-4, serum 25(OH)D (mean±SD) found to be 12.47±4.52 ng/ml in hip fracture group which is significantly lower than control group levels i.e. 17.57±5.21 ng/dl. (P value=0.018).

As shown in table-5, the Serum PTH (mean±SD) was 62.74±21.05 pg/ml among hip fracture case group significantly higher than of control group which was found to be 44.43±16.07 pg/ml. (P value<0.001).

As shown in table-6, the percentage of cases with abnormally increased serum PTH was more in case group as compared to control group (53.13% vs 14.06%; P Value<0.001) according to mean.

As shown in table-7, serum calcium (mean±SD) was 9.09 ±0.41 mg/dl in hip fracture case group which was significantly higher than in control group level i.e. 8.91±0.32 mg/dl. (P=0.007S)

As shown in table-8 Serum Alkaline Phosphatase (mean±SD) was significantly higher in hip fracture case group (129.27±10.42) than in control group (123.92± 10.78). (P value=0.005)

As depicted in table-9, a significant negative correlation between serum 25(OH)D and PTH existed in the control group (r= -0.636 moderate, P<0.001). A significant negative fair correlation between serum 25(OH)D and S. Alkaline Phosphatase (IU/Lt) existed in the control group. (r= -0.384, P=0.002). A non-significant positive poor correlation of vitamin D exist with S. Calcium in control group (r= 0.115, P=0.366). A non-significant positive poor correlation of vitamin D exist with age in control group (r= 0.014, P=0.91).

As shown in table-9, a significant negative correlation of serum 25(OH)D exist with PTH (r= -0.696 moderate, P<0.001) and with S. Alkaline Phosphatase (r= -0.274, P=0.029) in the case group. A significant positive poor correlation of vitamin D level exist with S. Calcium (r= –0.269, P=0.032). A non-significant positive poor correlation of vitamin D level exist with age (r= -.078, P=0.542).

As shown in table-10, a non-significant poor negative correlation exists between age and serum PTH level in group B i.e. the elderly subjects without fragility hip fracture.

Age Group	Case		Control		Total	
	No	%	No	%	No	%
60 to 64	13	20.31	21	32.81	34	26.56
65 to 69	22	34.38	20	31.25	42	32.81
70 to 74	10	15.63	13	20.31	23	17.97
75 to 79	9	14.06	7	10.94	16	12.50
≥80	10	15.63	3	4.69	13	10.16
Total	64	100.00	64	100.00	128	100.00
Chi-square = 6.388 with 4 degrees of freedom; *P = 0.172*						

Table-2: Distribution according to age of the cases and control subjects

Vitamin D level	Case		Control		Total	
	No.	%	No.	%	No.	%
<5 ng/ml	3	4.69	0	0.00	3	2.34
10 to 20 ng/ml	37	57.81	38	59.38	75	58.59
5 to 10 ng/ml	18	28.13	6	9.38	24	18.75
20 to 30 ng/ml	6	9.38	19	29.69	25	19.53
>30 ng/ml	0	0.00	1	1.56	1	0.78
Total	64	100	64	100	128	100
Chi-square = 16.773 with 4 degrees of freedom; P = 0.002						

Table-3: Distribution of the subjects according to Vitamin D Status

DISCUSSION

In our study it is observed that both the hip fracture group and control group are comparable in terms of age. As evident from our results, Majority of our study subjects were either elderly retired persons or housewives which remain housebound with minimal outdoor activities and least exposure to direct sunlight. We estimated a high prevalence of vitamin D deficiency in both study cohorts however the prevalence of vitamin D deficient subjects was much higher (90.65%) in hip fracture group than in control group (68.75%). The mean serum 25(OH)D

Vitamin D (ng/ml)						
Group	N	Mean	Minimum	Maximum	Std. Deviation	P value LS
Case	64	12.475	4.5	24.5	4.52	
Control	64	17.575	5.8	30.1	5.21	0.018
Total	128	15.025	4.5	30.1	5.49	

Table-4: Vitamin D status among study groups

PTH (pg/ml)						
Group	N	Mean	Minimum	Maximum	Std. Deviation	P-value
Case	64	62.74	26.60	105.00	21.05	<0.001
Control	64	47.43	15.30	85.60	16.07	
Total	128	55.08	15.30	105.00	20.18	

Table-5: Serum PTH status among study groups

(mean±SD) was 12.47±4.52 ng/ml in hip fracture group which is significantly lower than control group levels i.e. 17.57±5.21 ng/dl. These results were in accordance to the previous studies done in Indian population.[7-9]

When sunshine exposure is not adequate, dietary compensation for vitamin D should occur. Vitamin D intake in the elderly is around 100 IU/d or less in most European countries[1] and much lesser in Asian and southern countries. Fatty fish, such as herring, mackerel and salmon are a very rich source of vitamin D,[1,2] but are rarely eaten by the elderly in north Indian region. Food in India is not fortified with vitamin D, unlike other countries, for example, margarine in the UK and The Netherlands (usually 3 IU/g) and milk in the US (usually 400 IU/quart). So the dietary supply of vitamin D depends more or less on dairy products in Indian subjects and adequacy of dietary compensation can only assured when these are taken regularly in balanced diet.

Secondary hyperparathyroidism due to hypovitaminosis D has been proved to be principal mechanism by which means there is cortical bone loss and subsequent fragility fractures. Many investigators have observed increased serum PTH concentrations in elderly people with or without hip fractures associated with vitamin D deficiency.[1,2,10,11] In our study the mean Serum PTH (mean±SD) was 62.74±21.05 pg/ml among hip fracture case group significantly higher than of control group which was found to be 44.43 ±16.07 pg/ml. More importantly we had 53.13% of the cases with abnormally increased serum PTH in hip fracture case group as compared to only 14.06% in control group according to mean and this difference is also found to be statistically significant which further supports the role of secondary hyperparathyroidism in etiology of non-traumatic hip fractures.

Serum PTH correlated negatively with serum 25(OH)D in many studies,[1,5,12,13] usually with a correlation coefficient between 0.20 and 0.30. In our study as evident from the results there is a strong negative correlation between serum 25(OH)D levels and PTH in both hip fracture group (r=−0.696) and control group (r=−0.636) and it was found to be significant statistically. It signifies that in

	Case		Control		Total	
PTH	**No**	**%**	**No**	**%**	**No**	**%**
Increased values	34	53.13	9	14.06	43	33.59
Normal	30	46.88	55	85.94	85	66.41
Total	64	100	64	100	128	100
Chi-square = 20.172 with 1 degree of freedom; P < 0.001						

Table-6: Distribution of the subjects according to Serum PTH status

S. Calcium (mg/dl)						
Group	**N**	**Mean**	**Minimum**	**Maximum**	**Std. Deviation**	**P value**
Case	64	9.09	8.50	10.10	0.41	0.007
Control	64	8.91	8.40	9.80	0.32	
Total	128	9.00	8.40	10.10	0.38	

Table-7: Distribution of the subjects according to Serum Calcium levels

S. Alkaline Phosphatase (IU/Lt)						
Group	**N**	**Mean**	**Minimum**	**Maximum**	**Std. Deviation**	**P value**
Case	64	129.27	106.00	145.00	10.42	0.005
Control	64	123.92	101.00	147.00	10.78	
Total	128	126.59	101.00	147.00	10.89	

Table-8: Distribution of the subjects according to Serum Alkaline Phosphatase level

Correlations: Case Group					
		Age	**PTH (pg/ml)**	**S. Calcium (mg/dl)**	**S. Alkaline Phosphatase (IU/Lt)**
Vitamin D (ng/ml)	Pearson Correlation	.078	-.696**	.269*	-.274*
	Sig. (2-tailed)	.542	.000	.032	.029
	N	64	64	64	64
Correlations: Control Group					
		AGE	**PTH (pg/ml)**	**S. Calcium (mg/dl)**	**S. Alkaline Phosphatase (IU/Lt)**
Vitamin D (ng/ml)	Pearson Correlation	.014	-.636**	.115	-.384**
	Sig. (2-tailed)	.910	.000	.366	.002
	N	64	64	64	64

Table-9: Correlation of Vitamin D level with age, PTH, S. calcium and S. Alkaline phosphatase

Control	**Mean**	**Std. Deviation**	**N**	**R**	**R Square**	
Age	**67.47**	**5.77**	**64**			**Sig. F Change**
PTH	47.43	16.07	64	-.021[a]	.000	.872
Case	Mean	Std. Deviation	N	R	R Square	
Age	69.63	6.80	64			Sig. F Change
PTH	62.74	21.05	64	-.176a	.031	.164

Table-10: Correlation between age and S. PTH (control and case group)

geriatric population which frequently suffers from vitamin D deficiency there is consequent stimulation of parathyroid glands resulting into hyperparathyroid state and resultant cortical bone loss which may severe enough to produce fragility fractures.

Apart from secondary hyperparathyroidism osteomalacia due to deficient vitamin D and resultant unmineralized excessive osteoid tissue (hyperosteoidosis) may be the contributory factor in the causation of fragility fractures. Hyperosteoidosis can be accurately assessed by tetracycline labeled bone biopsy.[14] Because it is not possible for us to administer tetracycline in a fragility fracture patient before fracture happens, so the histological diagnosis of osteomalacia in such patients is not possible. However some investigators used to measure serum alkaline phosphatase levels for assessment of hyperosteoidosis but there may be false positive results.[15] We investigated the study groups with serum alkaline phosphatase and found that the mean serum alkaline phosphatase level was (mean±SD) 129.27 ±10.42 in hip fracture case group significantly higher than in control group (123.92± 10.78 IU/L). While correlating serum alkaline phosphatase levels with 25(OH)D levels there was a significant negative correlation of fair degree among both hip fracture cases and control group subjects which supports there should be an element of hyperosteoidosis in causation of fragility fractures.

Another important cause of hyperparathyroidism in geriatric patients is renal function impairment which may be caused due to hypocalcaemia via feedback mechanism or via direct effect of decreased levels of circulating vitamin D.[16] Hence there is decrease in renal calcitriol synthesis by 1α hydroxylase and an increased serum PTH levels which counters hypocalcaemic state in early stages of renal failure but all this happens at the price of increased bone turnover. Previous studies suggested decreased glomerular filtration rate with age and gradual increase in serum PTH with age.[17,18] In our study we correlated serum PTH levels with age data but we failed to find any significant correlation between them among both the case and control study groups.

Since the osteomalacia and secondary hyperparathyroidism are considered the consequences of poor calcium vitamin D nutrition and resultant hypocalcaemia; one can expect a lower serum calcium levels among fragility hip fracture individuals as described by some authors.[19,20] In our study the mean serum calcium was 9.09 mg/dl in hip fracture case group, and was marginally higher than control group which had a level of 8.91 mg/dl. Though this difference was statistically proven to be significant, but both the values lie in normal range of the serum calcium levels. The elevated levels of calcium among fracture group can be ascribed to the immobilization of patient and resultant mobilization of calcium from the bones.

With all of these considerations the results of our study indicate that the most appropriate 25-hydroxyvitamin D levels for our population should be higher than 30ng/ml. A decrease in serum vitamin D levels either by remaining housebound (hence low sunshine exposure), by decreased oral consumption of vitamin D2 or D3 or by depressed renal functions there may be activation of parathyroids which may lead to excess serum PTH and increased bone turnover and fragile bones. Deficient mineralization and defective skeletal muscle function may result into osteomalacia and frequent falls respectively, which aggravate the problem further. To avoid the above mentioned consequences we must revise our public health policy for assurance of adequate serum vitamin D levels among Indian population.

The major limitation of our study was that it includes a small sample size with patients either admitted or report to tertiary care centre which may not represent the population at large. Absence of bone mineral density results to support osteoporosis and false positivity among alkaline phosphatase results are other limitations. Further research with large scale population based studies is required to determine the exact correlation between vitamin D, serum PTH, bone histology and myopathy.

CONCLUSION

Our study highlights the high prevalence of hypovitaminosis D among geriatric Indian subjects, either that suffered from fragility hip fracture or apparently healthy. The increased percentage of vitamin D deficient subjects, the significantly reduced mean serum vitamin D levels among fragility fracture case group signifies that hypovitaminosis D is an important risk factor in causation of fragility fractures. Similarly significantly increased mean serum PTH levels and an increased ratio of hyperparathyroid individuals among fracture case group points towards role of secondary hyperparathyroidism among these study subjects. So, it can be concluded that supplementation of vitamin D and fortification of edibles with vitamin D for general population and population at risk might reduce the overall incidences of fragility hip fractures.

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