Unveiling the Metabolic Mystery of Fragility Hip Fracture in Indian Patients: A Histomorphometric and Biochemical Correlation

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Abstract

Background High prevalence of hypovitaminosis D is being reported in Indian patients with fragility hip fracture. The gold standard to diagnose osteoporosis and osteomalacia is bone histomorphometry. There is no study evaluating histopathological histomorphometry in Indian fragility hip fracture patients. The purpose of the study was to evaluate fragility hip fracture patients for histopathological osteomalacia and osteoporosis by histomorphometry and to correlate histopathological findings with biochemical hypovitaminosis D.

Materials and Methods A total of 55 patients of fragility hip fractures recruited for prospective cross-sectional study. During definitive fracture fixation of these fragility hip fractures, bone biopsy taken from neck region of femur by a novel approach for histomorphometry. Histomorphometric analysis was based on three indices, namely osteoid seam width, osteoblast surface, and osteoid surface. We also analysed blood bone biochemistry and correlated with bone histomorphometry.

Results In fragility hip fracture patients, the prevalence of histomorphometric osteoporosis and osteomalacia were very low (only 9.4% had osteoporosis and none had osteomalacia) however in blood bone biochemistry, we found high prevalence (85.5%) of hypovitaminosis D. We also noted significant changes when correlated bone histomorphometry with different blood bone biochemistry.

Conclusion Indian patients with fragility hip fracture were found to have high prevalence of biochemical hypovitaminosis D but unlike western literature, there was low prevalence of histomorphometric osteoporosis with no evidence of histomorphometric osteomalacia. Correct knowledge about metabolic status of fragility hip fracture is required to improve outcome, decrease complications and to optimise cost of the treatment.

Keywords Fragility hip fracture · Bone histomorphometry · Hypovitaminosis D · Osteomalacia · Osteoporosis

Introduction

Fragility hip fracture is a common orthopaedic injury. Surgery for fragility hip fracture is one of the most common orthopaedic operation performed worldwide including India, and

it affects all strata of society. Fragility fractures are fractures that result from ‘low energy’ trauma that would not ordinarily result in fracture. The World Health Organization (WHO) has quantified this as forces equivalent to fall from a standing height or less. Fragility fractures occur most commonly in

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the spine (vertebrae), hip (proximal femur), and wrist (distal radius) [1].

Association between hypovitaminosis D/osteomalacia and fragility hip fracture has been described only in few reports [2–5]. Patients with fragility hip fracture are at high risk of further fracture and it can be reduced by optimum metabolic therapy. But, treatment of metabolic component of hip fracture leaves a lot to be desired, and often arbitrary [6–8]. It is becoming more evident with continued research on fragility hip fracture that metabolic status of Indian patients is decidedly different from their western counterparts. Osteoporosis is known to be the major pathology associated with fragility hip fracture in western population [9, 10], but study in Indian patients has revealed disparate facts. Hip fractures occur at relatively earlier age in Indian patients. Most importantly, recent reports have described significant vitamin D deficiency in Indian and Asian population. Khadgawat et al. have reported very high prevalence of 96.7% of vitamin D deficiency in Asian-Indian patients with fragility hip fracture [11, 12]. It should be noted that serum vitamin D measurement cannot be used as a screening tool to diagnose osteomalacia [13]. The gold standard investigation to determine osteomalacia [3, 14] and osteoporosis [15] is bone histopathology. We have used a simple but novel approach to get biopsy for histomorphometric study, while operating fragility hip fractures.

Materials and Methods

It was a prospective cross-sectional descriptive study. The aim of the study was to evaluate histomorphometric and biochemical bone quality in patients with fragility hip fracture. The main objective was to determine the prevalence rates of histopathological osteomalacia and osteoporosis by bone histomorphometry, and biochemical hypovitaminosis D in fragility hip fracture patients, and to study their correlation. This study was conducted according to the Declaration of Helsinki. The study was approved by the Ethics Committee of the Institute and informed consent was obtained from all patients. All the patients presented to this institute with fragility hip (intertrochanteric and neck of femur) fracture were recruited by non-probability consecutive sampling. Study population included all the patients of fragility hip fracture admitted to Orthopaedics ward of the institute. The study started in June 2015 and the study period was around 18 months determined by calculated sample size and based on patient recruited depending on inclusion and exclusion criteria. For calculation of sample size, the formula applied:

$$n = 4 \frac{pq}{E^2},$$

where, n = sample size, p = estimate of prevalence from previous studies, $q = 1 - p$, E = maximum allowable error, which was taken as 5% of p

One study from India has reported prevalence of 96.7% for hypovitaminosis D [11]. We have taken this as yardstick for calculation of sample size. Therefore, by putting the values of $p = 0.967$, $q = 0.033$ and $E = 0.05$, the minimum required sample size was calculated to be 51. We studied total of 55 patients.

We employed precise inclusion and exclusion criteria to remove all the known confounding variables of osteoporosis and osteomalacia. Inclusion criteria included patients with fragility hip fracture aged 50 and above and presenting within one week of sustaining trauma. Exclusion criteria comprised of nonambulatory patients (before sustaining fracture), all fractures due to high energy trauma (road traffic accident, fall from height etc.), patients on calcium or vitamin D supplementation or on anti-osteoporotic medications, or any medications affecting calcium or vitamin D metabolism like steroids (if taken for more than 2 weeks in last 6 months) [16], anticonvulsants, antitubercular, anti-cancer, antiretroviral and anticoagulants etc. Also excluded were the patients with previous history of fractures of hip, spine, wrist or forearm, any history of uncorrected refractive errors or with altered mental status. Patients with systemic illnesses interfering directly with bone metabolism like primary hyperparathyroidism, chronic kidney diseases (serum creatinine > 1.5 mg/dL), chronic liver disease (raised serum transaminases/bilirubin), malignancy, inflammatory bowel disease and any bowel resection surgery etc. were also excluded.

Collected blood investigations included markers of bone metabolism namely serum alkaline phosphatase (SAP), serum calcium, serum 25 (OH) vitamin D3 and serum 'intact' parathyroid hormone (PTH). Serum level of 25 (OH) vitamin D3 was checked using electro chemiluminescence immunoassay system (Beckman Coulter Access 2). For fracture classification, X-ray of the concerned hip, anteroposterior and lateral views were taken. Fragility hip fractures patients were operated as per the standard principles of Orthopaedic surgery. All femoral neck fractures underwent uncemented/cemented modular bipolar prosthesis. Our institute is a tertiary care Central Government Institute and orthopaedic implants are procured by central rate contract. During the period of the study, dynamic hip screw (DHS) was approved and available for intertrochanteric fractures of femur. For intertrochanteric fractures, bone biopsy was taken after drilling through triple reamer, and before tapping for putting lag screw. Bone was curetted from inferior part of drilled neck region by using 5 mm oval bone curette. Thereafter, neck was tapped to ensure proper placement of lag screw. For neck of femur fracture, biopsy was taken from calcar part of the neck by bone nibbler. We stopped study

when total of 55 bone biopsies were taken and sent to pathology department. Histopathological evaluation was performed on non-decalcified bone specimen by bone histomorphometry using ‘Dewinter Premium LED microscope with Biowizard software for histomorphometry’ and was reported as normal bone quality (Fig. 1) or pathological (Fig. 2) i.e. osteomalacia or osteoporosis. Osteomalacia was diagnosed if average thickness of osteoid was more than 20 microns (normal 15 ± 2.3 microns) and over 20% of bone surface covered by osteoid (normal $2.1 \pm 1\%$). Osteoporosis was reported if they have at least two out of three positive histological evidences (of osteoporosis) namely (1) osteoid seam width (average thickness of the osteoid seam) $< 8.8 \mu\text{m}$, (2) osteoid surface (fraction of the trabecular bone lined by osteoid seams) $< 20\%$ and (3) osteoblast surface (fraction of the trabecular bone lined by osteoblasts) $< 20\%$ [3, 14, 15].

Vitamin D status was classified based on 25(OH) Vitamin D level. It was reported as vitamin D deficiency ($< 50 \text{ nmol/L}$), severe deficiency ($< 12.5 \text{ nmol/L}$), relative insufficiency ($50\text{--}70 \text{ nmol/L}$) and optimum level ($> 70 \text{ nmol/L}$) [4, 17, 18]. The reference range for normal SAP was taken as $70\text{--}140 \text{ IU/L}$, as dictated by our institutional reference range.

Along with proper history, patients were also asked about adequacy of sun exposure. Adequate sun exposure

was defined as around 2 h per week of outdoor activity during the summer with exposure of the face, hands and arms (approximately 25% of the body surface area) [19].

Result

Demographics

Total 157 patients with fragility hip fracture were presented to Orthopaedics Department during study period and were considered for study and after satisfying the inclusion and exclusion criteria 55 patients were finally included in the study. Out of included 55 patients, 32 were males and 23 females. 24 were intertrochanteric fractures and 31 were neck of femur fractures. The mean age of the patients was 65.29 years (range from 50 to 87 years). The mean ages of male and female patients were 65.97 and 64.35 years, respectively. All the patients included in the study reported non-sedentary lifestyle with adequate sun exposure.

Vitamin D Level

The mean 25 (OH) vitamin D3 level was $34.04 \pm 2.71 \text{ nmol/L}$ (range $4.9\text{--}109.6 \text{ nmol/L}$). Vitamin D deficiency was

Fig. 1 Microscopic image of normal bone histomorphometry (magnification 10×40 and scale in micrometer) showing osteoid seam (Yellow arrowhead) and osteoblast (black arrow)

Fig. 2 Microscopic image of osteoporotic bone histomorphometry (magnification 10×40 and scale in micrometer) showing neither osteoid seam over trabecular bone and nor any osteoblast visible. It has all the three histomorphometric positive criteria for osteoporosis

observed in 85.5% (47 patients), in which 13% (7 patients) were severely deficient. Optimum vitamin D level was detected in meagre 5.4% (3 patients) only. Age wise deficiency grading is also noted (Table 1). The box plot of vitamin D level (Fig. 3a), is showing majority of values are at lower level and only few specks of data in optimum range.

Serum Calcium, Alkaline Phosphatase and PTH

Mean serum calcium was found to be $8.6 \text{ mg/dL} \pm 0.06$ (range 7.6–9.6 mg/dL), with standard deviation of 0.49 and standard error of 0.06. The box plot showed symmetrically distributed values within narrow physiological limits and with no outliers (Fig. 3b). It is very much scientifically plausible as plasma calcium concentration is tightly controlled by a complex homeostatic mechanism. Surprisingly, serum alkaline phosphatase was elevated in all but one patient, and

the patient with normal ALP has normocalcemia (9.5 mg%) with vitamin D deficiency (31.75 nmol/L) and with normal PTH. Serum PTH was elevated in 3 patients. The biochemical characteristics of patients with elevated PTH are described (Table 2).

Biochemical Correlation

Pearson correlation coefficient was calculated between scientifically plausible parameters of biochemical bone quality to know the strength and direction of existence of any (linear) relationship between different variables.

Vitamin D (x) vs serum calcium (y): correlation coefficient = 0.185 (Fig. 4a).

Age (in years) vs vitamin D level (nmol/L): correlation coefficient = -0.039 (Fig. 4b).

Table 1 Age wise vitamin D deficiency

Age group	Severe vitamin D deficiency (< 12.5 nmol/L)	Vitamin D deficiency (< 50 nmol/L)	Relative insufficiency (50–70 nmol/L)	Optimum level (> 70 nmol/L)
50–59 years	2	15	2	1
60–69 years	2	13	1	
70–79 years	1	13	2	1
80 years and above	2	6	0	1

Fig. 3 Left image is box plot of vitamin D level showing majority of values are at lower level and only few values are in optimum range (a). Right image is box plot of serum calcium showing symmetrically distributed values within narrow physiological range and with no outliers (b)

Table 2 Biochemical characteristics of patients with elevated PTH

Patient no.	Age (years)	Sr. Calcium (mg/dL)	SAP (IU/L)	Vitamin D (nmol/L)	PTH (pg/mL)	Diagnosis
50	50	8.7	236	30.3	74.82	IT (R)
41	70	9	180	51.8	93.7	IT (L)
29	74	8.2	243	14.11	204.9	NOF (L)

Vitamin D (x) vs SAP (y) and PTH (x) vs SAP (y): correlation coefficient = -0.143 and -0.068 respectively (Fig. 5a, b).

Histopathological Histomorphometry for Osteomalacia and Osteoporosis

Despite the presence of 85.5% of hypovitaminosis D including 13% of severe deficiency, none of the patients showed any histological evidence of osteomalacia. Two of the specimens, one each of intertrochanteric and neck of femur fracture, were not evaluable may be because of bony necrosis resulting from crushing artefact. So, total of 53 bone biopsies were studied. The prevalence of osteoporosis defined on histological basis (Table 3) revealed histopathological

evidence of osteoporosis in five patients only (9.4%) out of which three patients showed 2 evidences and 2 patients showed all 3 evidences of histopathological osteoporosis (Table 4).

Correlation Between Biochemical and Histomorphometric Parameters

Correlation between biochemical parameters (Ca, ALP, 25(OH) D3 and PTH) and histomorphometric parameters (OSW, OST & OSB) of histopathological osteoporosis was done (Table 4). It is evident that there is high prevalence of biochemical hypovitaminosis D (85%), however very low prevalence of histomorphometric osteoporosis (9.4%).

Fig. 4 Image **a** showing correlation coefficient between Vitamin D (x) and serum calcium (y): (correlation coefficient = 0.185). Image **b** showing correlation coefficient between age (in years) vs vitamin D level (nmol/L): correlation coefficient = -0.039

Discussion

Although there is no consensus on optimal levels of 25 (OH) D3 as measured in serum, vitamin D deficiency is defined by most experts as a 25 (OH) D3 level of less than 50 nmol/L, whereas levels of 50–70 nmol/L, > 70 nmol/L and < 12.5 nmol/L are regarded as relative insufficiency, optimum level and severe deficiency, respectively [4]. As stated earlier, one study from India observed 96.7% (all patients except one) of patients with fragility hip fracture had vitamin D deficiency with mean vitamin D level of 25 ± 12 nmol/L [11]. Another 2 studies from India have reported the prevalence of hypovitaminosis D (cut-off 50 nmol/L) as 74%, in fragility hip fracture [17], and 82% in patients presenting with orthopaedic trauma [18], whereas, some other studies from Brazil, Egypt and China reported a prevalence of 54.5, 60.9 and 71.3% in fragility hip fracture, respectively [19]. The occurrence of hypovitaminosis D in fragility hip fractures, otherwise, is global. Many other studies have also reported presence of hypovitaminosis D in hip fracture [20]. There are various risk factors that have been described for hypovitaminosis D namely, older age, female gender, darker skin pigmentation, clothing and cultural

practices that determine sunlight exposure, dietary habits and presence of any national policy regarding vitamin D fortification [21]. A small standard error of 2.71 means that our sample was possibly true representative of the population for which the study was done [22].

We studied the correlation between different biochemical parameters. Vitamin D vs serum calcium showed very small positive correlation ($r = 0.185$). It is understandable because vitamin D increases serum calcium, but serum calcium is also regulated by PTH, calcitonin and other complex physiological events. SAP showed negative but very minuscule correlation with vitamin D ($r = -0.143$) and PTH (-0.068). This means that there is no reasonable relation of SAP with vitamin D or PTH. Some of the studies have also noted inverse correlation between level of SAP and vitamin D deficiency state [12]. Nevertheless, level of SAP was found to be raised in 98% of the patients (all but one). It is a non-specific marker and reason for its increased level may be multifactorial. Farek et al. also noted that alkaline phosphatase is not a predictor of degree of bone mineralization though it was reported in preterm infants [23]. Neither was any reasonable correlation observed between vitamin D and age of the patients ($r = -0.039$).

Fig. 5 Image **a** showing correlation coefficient between Vitamin D (x) and SAP (y): (correlation coefficient = -0.143). Image **b** showing correlation coefficient between PTH (x) and SAP (y): correlation coefficient = -0.068

Table 3 Histopathological prevalence of osteoporosis

Histopathological evidence of osteoporosis	Patients	
	No.	Percentage
Osteoid seam width (average thickness of the osteoid seam) $< 8.8 \mu\text{m}$	6	11.3
Osteoid surface (fraction of the trabecular bone lined by osteoid seams) $< 20\%$	6	11.3
Osteoblast surface (fraction of the trabecular bone lined by osteoblasts) $< 20\%$	5	9.4
Positive histological evidence of osteoporosis (a combination of two or three positive criteria above)	5	9.4

Now, after having discovered and understood the all-important and fortuitous information about hypovitaminosis D, can we move ahead more easily? This uncovering of new facts about hypovitaminosis D in fragility hip fracture is like finding a ‘trojan horse’ in our backyard, because it increases the dilemma of orthopaedic surgeons manifold! In this scenario, we need to understand the histopathological aspect of fragility hip fracture before starting optimum metabolic therapy.

We could not find any evidence of osteomalacia in our recruited patients. The reason may be that in order to remove all the possible confounding variables associated with osteomalacia, we used stringent exclusion criteria that excluded all possible systemic causes of osteomalacia. Secondly, we cater to the health needs of industrial workers

and their families and they are known to have physically active lifestyle. Knowledge about possibility of osteomalacia in fragility hip fracture is very important because all the non-invasive modalities of diagnosis of osteoporosis like DEXA (dual-energy X-ray absorptiometry), QCT (quantitative computed tomography), pQCT (peripheral quantitative computed tomography) etc. cannot differentiate between osteomalacia and osteoporosis and can result in inappropriate diagnosis and treatment [24]. In our study group, there were only five patients (9.4%) that satisfied the histopathological criteria of osteoporosis. The possible reason for finding such low prevalence of osteoporosis may be same as discussed for osteomalacia above. This finding of such low prevalence of osteoporosis should lead us to the hitherto ‘concealed axiom’ that not all fragility hip fractures are

Table 4 Composite table showing biochemical and histomorphometric parameters of histopathological osteoporosis [OSW: osteoid seam width (average thickness of the osteoid seam) < 8.8 µm, OST:

osteoid surface (fraction of the trabecular bone lined by osteoid seams) < 20%, OSB: osteoblast surface (fraction of the trabecular bone lined by osteoblasts) < 20%]

Patient No.	Age / Sex	Ca (mg/dl)	ALP (IU/L)	25(OH)D3 (nmol/L)	PTH (pg/ml)	Diagnosis	OSW	OST	OSB
3	87 / M	8.7	208	109.6	21.64	NOF (L)			
6	61 / F	8.4	147	14.96	29.74	NOF (L)			
12	75 / M	7.7	239	33.3	9.79	NOF (L)			
16	82 / F	8.8	352	30.1	10.87	IT (L)			
18	73 / M	7.9	832	32.8	13.89	IT (L)			
27	85/M	8.1	280	29.03	37.7	IT (R)			
28	80/F	8.8	242	7.5	20.41	IT (R)			
35	59 / F	7.6	372	7.5	11.26	NOF (R)			
43	69/M	8	222	24	11	IT (L)			
50	50/ F	8.7	236	30.3	74.82	IT (R)			
55	85 / M	8.1	320	44.9	4.41	NOF (R)			

Green cells indicate normal histomorphometry and red cells indicate that the stated parameter is positive for histomorphometric osteoporosis. Patients were labelled osteoporotic only if they had at least two out of three positive histopathological evidences of osteoporosis.

because of osteoporosis. Refusing to accept and implement this fact can lead to inappropriate treatment [25]. Second, bisphosphonates and related anti-resorptive pharmacotherapy may not be indicated in patients without osteoporosis and their exact role in these patients remains to be studied. In our opinion, there should not be ‘ritualistic’ prescription of antiresorptive therapy in fragility hip fracture. Third, these medications may add on to the potentially serious medication related side effects and complications. And Fourth, they can increase the cost of the treatment where resources are always scarce. Presence of histopathological osteoporosis does not correlate with any of the biochemical parameters studied, though serum calcium was at lower level and all patient but one showed deficiency of vitamin D.

So, in view of the discovered facts, we recommend that all patients should be assessed for osteoporosis before starting anti-resorptive treatment. As researcher we have the privilege to exclude patients based on their medical condition for the study, but unfortunately patient cannot choose their medical condition. Though we couldn’t find any patient of histopathological osteomalacia possibly because of stringent study criteria and some amount of inadvertent selection bias because our cohort of patients were physically more active, there is always possibility of osteomalacia depending on their medical condition or history of chronic medication use. Secondly, our another hypothesis for absence

of histopathological osteomalacia is that the ‘pathological bone’ fractures before the limits of detectable histopathological osteomalacia sets in. So, we recommend histomorphometry in patients with fragility hip fracture to correctly diagnose the metabolic disorder, though presently this modality is not widely available and is limited to academic and research work.

Our second recommendation is that all fragility hip fracture patients should be screened for hypovitaminosis D and optimum replacement therapy should be provided. There are plenty of reports observing insufficient treatment of metabolic aspect of hip fracture, mainly due to lack of insight and failure to recognize this possibility after surgical management of hip fracture [8]. Vitamin D is not only important for bone health, but also it has multiple extra-skeletal benefits including direct effect on mortality [26]. The non-skeletal health benefits of optimum vitamin D status include cancer chemoprevention, activation of the innate immune system, decrease in the risk of autoimmune diseases, better metabolism with optimum cardiovascular health and prevention of diet-induced obesity, improvement of muscle function of elderly and reduction in the risk of falls by about 20% [27].

Most importantly, in the context of rehabilitation of operated fragility hip fracture patients, its replacement is especially important as vitamin D sufficiency improves muscle function and power, which are required for proper

rehabilitation of these patients [17]. More recently, Lavernia et al. have reported lower hip replacement functional scores in hypovitaminosis D, that improves with vitamin D replacement [28].

For replacement of vitamin D, 60,000 units PO weekly for 6–8 weeks is suitable and is unlikely to induce hypervitaminosis in patients who have not received any previous treatment [29]. If compliance is issue, loading dose is strongly recommended. The REVITAHIP study has shown that in older patients following hip fracture surgery, a loading dose of 250,000 IU vitamin D3 (“Active”) compared with placebo, followed by treatment with vitamin D (800 IU) and calcium (500 mg) daily in both groups, resulted in higher 25-OHD levels and a greater percentage with target ‘sufficient’ 25-OHD levels [30]. We routinely advise 3 to 6 lakhs of loading dose of cholecalciferol if there is doubt about compliance and if there is no medical contraindication like poorly controlled hypertension, certain heart conditions, recent history of renal stones etc. Till now we have not observed any undesired effect. Vitamin D toxicity is observed when serum level of 25-hydroxyvitamin D is greater than 374 nmol/L (150 ng/mL). Vitamin D toxicity with oral replacement treatment is a rare event and generally is due to dispensing error or accidental ingestion. There is no consensus regarding upper safe limit, but doses up to 10,000 units/day may be safely tolerated for limited duration in selected indications [4, 31].

Conclusion

Indian patients with fragility hip fracture have high prevalence of hypovitaminosis D but no histopathological evidence of osteomalacia, in absence of predisposing medical comorbidities. We also observed low prevalence of osteoporosis in our patients. These histopathological findings may be due to very stringent exclusion criteria we employed in order to decrease the effects of confounding variables. Additionally, there may have been inadvertent cluster sampling error as our cohort of patient were from physically active social profile. Similar studies from other centres will shed more light. We recommend routine screening of patient for hypovitaminosis D and vitamin D replacement therapy before starting anti-resorptive treatment, if indicated. We also recommend routine use of histopathology to accurately diagnose the metabolic status and to implement optimum treatment.

Author contributions MNA: Study design, Analysis of Data, Carried out the surgery, Removal of material with gross examination of tissue to be sent for Histopathological examination, Supervised the study, Preparation of manuscript and reviewed the manuscript. SG: Gross and Histopathological examination of tissue sent for Histopathological

examination with its reporting, Preparation of photograph of Histopathological examination. BS: Helped in Study design, Data collection, Preoperative investigation and surgical intervention. LK: Helped in Study design, surgical intervention and follow-up of patients. RB: Helped in Study design, Preoperative investigation, surgical intervention, Data collection, and Preparation of manuscript. SK: Study design, Analysis of Data, Supervised the study, and reviewed the manuscript for final preparation. This manuscript represents the honest work performed in our institute. All the authors have approved this final manuscript and agreed to submit to the Indian Journal of Orthopaedics.

Compliance with Ethical Standards

Conflict of interest All the authors declared that there is no conflict of interest.

Ethical standard statement Ethics committee approval number: 412 (DEAN-JOKA)/IEC/2014-15/Vol I.

Informed consent For this type of study informed consent is not required.

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