Indian Journal of Orthopaedics (2021) 55:614–620
https://doi.org/10.1007/s43465-020-00323-z

ORIGINAL ARTICLE

Coexistence of Osteomalacia in Osteoporotic Hip Fractures in More Than 50 Years Age Group

Karmesh Kumar[1] · Himanshu Bhayana[1] · Kim Vaiphei[2] · Devendra Chouhan[1] · Rajendra Kumar Kanojia[1] · Sanjay Bhadada[3]

Received: 13 July 2020 / Accepted: 28 November 2020 / Published online: 15 January 2021

Abstract

Introduction Osteomalacia is a hitherto common orthopaedic condition and is commonly coexists with osteoporosis. However, the identification of osteomalacia always slips under the radar and more emphasis is given to diagnosis and management of osteoporosis. Identification of osteomalacia is equally relevant as management of the osteoporotic fractures is different with or without osteomalacia

Methods This was a prospective study design that included patients 50 years or above of either sex presented with proximal femur fractures. Osteoporosis was identified by DEXA scan of hip and lumbar spine. Metabolic tests including serum calcium, phosphorus, ALP and vitamin D levels were done. Histopathological diagnosis of osteomalacia was performed on bony tissues that were taken during surgery from a site adjacent to the fracture and histological examination was performed on non-decalcified paraffin sections using special stains.

Results A total of 45 patients was included in study. Mean age was 68.7 years (53–85 years). Abnormal values of serum calcium, phosphorus, ALP, vitamin D were noted in 44.4%, 22.2%, 53.3% and 48.9% patients, respectively. On histopathology, 73.17% patients showed osteomalacia. No significant correlation was found between serum biochemical markers and histopathology except with serum Vitamin D (p value − 0.004).

Conclusion The majority of patients with osteoporotic hip fractures had coexisting osteomalacia. Abnormal biochemical values were not significantly associated with osteomalacia. Hence, histopathology remains the gold standard for the diagnosis of osteomalacia. Further research is needed to identify a biomarker that may enable the clinician to diagnosis and treat osteomalacia well in time.

Keywords Osteomalacia · Osteoporotic hip fracture · Vitamin D deficiency · Bone mineral density · Bone health

Introduction

Osteomalacia is characterized by defective or delayed bone mineralization [1] resulting in low bone mineral density (BMD). It is mainly due to Vitamin D deficiency [2] (VDD) and is widely prevalent in countries such as India where majority of population receives suboptimal nutrition [3]. High prevalence of VDD has been reported in healthy Indian subjects among all age groups [4]. This includes both urban and semi-urban Indians, postmenopausal women, pregnant

✉ Rajendra Kumar Kanojia
drkanojia_rajendra@yahoo.co.in

Karmesh Kumar
karmeshbeniwal@gmail.com

Himanshu Bhayana
himanshu.bhayana.mamc@gmail.com

Kim Vaiphei
kvaphei2009@gmail.com

Devendra Chouhan
drdevnim@gmail.com

Sanjay Bhadada
bhadadask@rediffmail.com

[1] Department of Orthopaedics, PGIMER, Chandigarh 160012, India

[2] Department of Histopathology, PGIMER, Chandigarh 160012, India

[3] Department of Endocrinology, PGIMER, Chandigarh 160012, India

women, school children and newborns [5, 6]. A prospective observational study was carried out from July 2006 to March 2008 by Khadgawat et al [7] on Indian patients with osteoporotic hip fractures. The authors reported all patients ($n=43$) except one had VDD.

Another metabolic disease common in India is osteoporosis. In 2013, around 50 million people in India were reported to have osteoporosis [8]. Fractures of femur neck and intertrochanter region were the most commonly reported osteoporotic fractures and add significant health burden [9]. Various studies have documented that osteomalacia and osteoporosis coexist especially in elderly population [10, 11].

Identification of osteomalacia is a challenging situation especially if it co exists in the setting of osteoporosis. The symptoms, such as bone pain, decreased bone radio-density and increased risk of bone fractures mimic each other [12]. Secondly, for diagnosis of osteomalacia, blood tests alone are not sufficient [13], and the gold standard is bone histopathology [14]. Indeed, identification of osteomalacia cannot be overemphasised especially in patients with fracture because correction of osteomalacia component promotes fracture healing [15, 16]. Yet the orthopaedic community do not stress on identification of osteomalacia despite its significance. The aim of this study was to identify the coexistence of osteomalacia in osteoporotic hip fracture patients in more than 50 years age group.

Methods

Patient Selection

This was a prospective study conducted at Level 1 trauma centre in North India done in July 2015 to June 2016. Patients 50 years or above of either sex, who presented to the orthopaedics department with hip fractures, i.e., fracture neck of femur and intertrochanteric having a t score of less than -2.5 based on DEXA scan was considered for the study. Patients in whom biopsy could not be performed, patients with fracture due to secondary osteoporosis (hyperparathyroidism and other endocrinopathies, drugs, malabsorption syndrome, chronic kidney disease, haematological disorders, etc.) metastatic hip fractures, and patients not willing to be part of the study were excluded. Patients with a history of calcium and vitamin D supplementation were also included in the study, but patients with a history of bisphosphonate were excluded. Besides the routine clinical documentation of history and examination, relevant history was also obtained for the presence of any co-morbidities, nutritional habits and history of sufficient sunlight exposure (exposure of both hands and face to direct sunlight, without any clothing, for 15–20 min daily for 5 days a week was considered as sufficient sunlight exposure) [17], family history for any significant congenital or genetic disorders. Fasting venous blood samples were collected within 24 h of hospital admission for routine hemogram, serum calcium, phosphorus alkaline phosphatase (ALP), Vitamin D (serum 25[OH] D), intact parathyroid hormone (iPTH), HbA1c for glucose level, antitissue transglutaminase antibody (anti-tTG) level for celiac disease, liver and kidney function tests. Patients with normal values of iPTH were included in the study. Serum calcium level was adjusted according to the serum albumin levels. Corrected calcium (mg/dl) = (normal serum albumin level − patient's serum albumin level) × 0.8 + measured total calcium level. DEXA scan of spine and hips were carried out routinely in all enrolled patients. Modality of the surgical treatment was determined depending on the configuration fracture and bone quality either by cephalomedullary nailing or dynamic hip screws or bipolar hemi-arthroplasty. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in study. Prior institutional clearance was obtained from IRB (institutional review board) vide infra: NK/2255/MS/10823-24.

Histopathological Examination

Samples for histopathology were collected at the time of operation from the affected site and adjoining area of the size of around 1 cm in separate vials containing absolute alcohol. All biopsies were processed as such without decalcification after overnight fixation. Sections of 3- to 5-micron thickness were stained with routinely with H&E, toluidine blue at pH 2.8, elastic von Gieson, Masson's trichrome and Solochrome cyanine R. Biopsies were assessed by (a) studying overall contour of bony trabeculae, i.e., normal thickness or thinning of trabeculae. If thinning of the trabeculae was observed, grading as mild, moderate, or gross/extensive was done subjectively and also extent of involvement of the bony areas, i.e., focal/patchy or diffuse/extensive was documented. (b) Reduced calcification of the bony trabeculae was graded into mild, moderate and severe. Comments were also made for non-calcified osteoid front of bony trabeculae, osteoblastic and osteoclastic giant cells, inter-trabeculae areas for fibrosis and granulation tissue. A biopsy showing mainly collagenised tissue was not graded. Histological parameters were interpreted in context to normal bone section obtained along the resection margins of limb amputation for fresh traumatic injury or malignancy.

Statistical Analysis

The investigation parameters were analysed by statistical software SPSS 22.0 version. Mean and standard deviation of variables were calculated, and the correlation to histopathology was done using Pearson's correlation method. Statistical significance was set at $p < 0.05$. For the calculation of sample size, we used statistical formula. In the previous studies, prevalence of osteomalacia in osteoporotic hip fractures among more than 50 years age of population was from 30 to 65% [10, 11]. In the current study, we recruited 45 patients (sample size using below formula was 42.68) assuming that prevalence of osteomalacia in osteoporotic hip fractures among more than 50 years age of population as 50% at our setting and absolute precision as 15% with 95% confidence interval.

$$n_0 = (1.96)^2 PQ / D^2.$$

Here n_0 is the sample size, P is the prevalence of osteomalacia in osteoporotic hip fractures among more than 50 years age population, i.e., 50% = 0.50, Q = 1 − P = 1 − 0.50 = 0.50, D is the Absolute precision, i.e., 15% = 0.15.

Results

A total of 45 patients was included in the study. The demographic and fracture characteristics are shown in Table 1. 84.4% patients ($n = 38$) sustained fracture at home with fall/slip in the bathroom or wet floor. As per dietary habits, 75.6% patients ($n = 34$) were vegetarian and 24.4% ($n = 11$) were non-vegetarian. 13.3% patients ($n = 6$) were smokers and 20% patients ($n = 9$) were chronic alcoholic. Only 42.2% patients ($n = 19$) had history of sufficient sunlight exposure. No patients were family history of congenital or genetic disorders. Among co-morbidities 64.4% patients ($n = 29$) were hypertensive while 40% ($n = 18$) were diabetic. Mean BMD value at spine was 0.700 ± 0.148 g/cm^2 and mean value at hip was 0.594 ± 0.156 g/cm^2. 4 (8.9%) patients were presented with a history of calcium and vitamin D supplements and 7 (15.6%) patients were history of previous osteoporotic fracture, but not on anti-resorptive medications like bisphosphonates.

Low values of serum calcium, phosphate, $Ca \times PO_4$ product and Vitamin D was found in 44.4% ($n = 20$), 22.2% ($n = 10$), 42.2% ($n = 19$) and 53.3% ($n = 24$) patients, respectively. Serum ALP level found high in 53.3% ($n = 24$) patients (Table 2).

Osteomalacia was established on histopathological analysis in 30/41 (73.2%) cases, of these, 3/30 (10%) cases had mild, 8/30 (26.7%) cases had moderate and rest 19/30 (63.3%) cases had severe osteomalacia (Fig. 1). 4 cases biopsy specimen showed dead or fibrous tissues.

For correlation, we excluded those four cases and the histopathological and biochemical correlation was obtained for the remaining 41 patients (Table 3). No significant correlation was found with serum biochemical markers except with serum Vitamin D (p value −0.004) (Fig. 2). Out of 29/41 (70.7%) intertrochanteric fractures patients, osteomalacia were established in 22 (53.6%) patients while patients with neck femur fractures ($n = 12$; 29.3%), osteomalacia were established histopathologically in 8 (19.5%) patients. Amongst 78.1% vegetarian patients ($n = 32$), 63.4% patients ($n = 26$) had osteomalacia. ($p = 0.042$) and amongst 56.1% female patients ($n = 23$), 46.3% patients ($n = 19$) had osteomalacia ($p = 0.164$).

Table 1 Patients demographic data and fracture characteristics

Total no. of patients	45
Mean age	68.7 ± 8.5 years (53–85 year)
Mean BMI	21.7 ± 3.2 kg/m^2
Sex	
Male	20 (44.4%)
Female	25 (55.6%)
Type of fracture	
I/T[a]	31 (68.9%)
NOF[b]	14 (31.1%)
Side of fracture	
Left	28 (62.2%)
Right	17 (37.8%)
Dietary habits	
Vegetarian	34 (75.6%)
Non-vegetarian	11 (24.4%)
H/O previous osteoporotic fractures	7 (15.6%)
H/O calcium and vitamin D supplementation	4 (8.9%)

[a]Intertrochanteric fracture

[b]Neck of femur

Discussion

Osteomalacia is defined as defective mineralization of bone matrix. The main cause of osteomalacia is vitamin D deficiency that can be due to nutritional deficiency, reduced cutaneous production, malabsorption, chronic liver diseases and long-term anticonvulsive therapy [18]. Several studies have showed that bone mineral density (BMD) is markedly reduced in osteomalacia bone [19, 20] and display similar clinical features, such as bone pain, decreased bone radio density and increased risk of bone fractures, as seen in osteoporosis. Histopathological diagnosis is essential to

Table 2 Level of various biochemical values among patients

Biochemical markers	Number of patients	Mean ± SD[a]
Serum calcium (8.8–10.2 mg/dl)		
Normal/high	25 (55.6%)	8.7 ± 0.45 mg/dl
Low	20 (44.4%)	
Serum phosphorus (2.7–4.5 mg/dl)		
Normal/high	35 (77.8%)	3.2 ± 0.56 mg/dl
Low	10 (22.2%)	
Serum ALP[b] (42–128 U/L)		
Normal	21 (46.7%)	133.6 ± 49.97 U/L
High	24 (53.3%)	
Ca × P product (27–32 mg/dl)		
Normal/high	26 (57.8%)	28.45 ± 5.59 mg/dl
Low	19 (42.2%)	
Corrected calcium (8.8–10.2 mg/dl)		
Normal/high	25 (55.6%)	9.2 ± 0.67 mg/dl
Low	20 (44.4%)	
Serum vitamin D (10.0–42.9 ng/ml)		
Normal/high	21 (46.7%)	13.23 ± 9.64 ng/ml
Low	24 (53.3%)	

[a]Standard deviation

[b]Alkaline phosphate

differentiate between osteoporosis and osteomalacia because no other single blood screening test is sufficient for establishing the diagnosis. In our study, osteomalacia was established in 30 out of 41 cases (73.2%). Tucker et al. [10] in 1988 found that amongst osteoporotic hip fractures, osteomalacia was found in 65.4% ($n = 17/26$) patients. Another study by Hordon et al. [11] were showed that overall 12% ($n = 9/72$) prevalence of osteomalacia in elderly femoral neck fracture patients Several other studies also showed the presence of osteomalacia in bone biopsies from proximal femur fracture patients [21, 22].

Serum calcium and vitamin D level plays an important role in finding out status of bone health [23]. Serum 25 [OH] D levels is most practical and widely used parameter to assess vitamin D status of an individual. There is no generally accepted criteria on optimal levels of serum 25[OH] D level, VDD is defined [2] as serum vitamin D level < 20 ng/ml. Using this cutoff value, we found 80% patients had VDD, and we found 53.3% patients below 10 ng/ml (severe VDD). A study by Peacey et al. [13] reported that relying solely on routine biochemical laboratory tests like serum calcium, phosphate and alkaline phosphatase can lead to missed diagnosis of osteomalacia in about 20% of cases. In our study, low level of serum calcium, serum phosphorus and Ca x P product was found in 44.4%, 22.2% and 42.2% patients, respectively. Raised level of serum ALP was found in 53.3% patients.

The majority of patient's dietary habits were vegetarian and amongst female patients, many were post-menopausal. Body weight, age, menopause and calcium intake are important determinants of BMD and healthy lifestyle (such as diet, exercise and sunlight exposure) plays an important role [24]. Adequate intake of calcium and vitamin D increases bone mass and prevents long-term fracture risk in postmenopausal women [25]. Only 8.9% of our study patients were taking regular vitamin D and calcium supplementation at the time of sustaining hip fracture.

The treatment approach for patients suffering from these two similar types of metabolic bone diseases is different. Osteoporosis treatment mainly aims about removing all risk factors, supplementing vitamin D3 (600-800 IU/days), calcium (dietary calcium 1200 mg/days) and anti-resorptive therapy [26]. The main aim of osteoporosis treatment is decreasing fracture risk, which can be achieved by bisphosphonates, anti-resorptive drugs so these called gold standard for treating osteoporosis [27]. However, management of osteomalacia involves giving vitamin D3 and calcium for at least 1 or 2 years [28]. It is noted that with proper treatment of osteomalacia, normalization of BMD of vertebrae and hip is expected to be reached in up to 12 months [29]. Some studies suggest that increasing doses of Vitamin D for treatment of patients with osteoporosis [23, 28, 30], is also useful for accompanying some cases of subclinical osteomalacia.

Our study is not without its share of limitations. We do not have a very large sample size, so it may not truly be a reflection of actual incidence of whole Indian population, besides we did not study for any relevant haematological markers of bone formation and resorption.

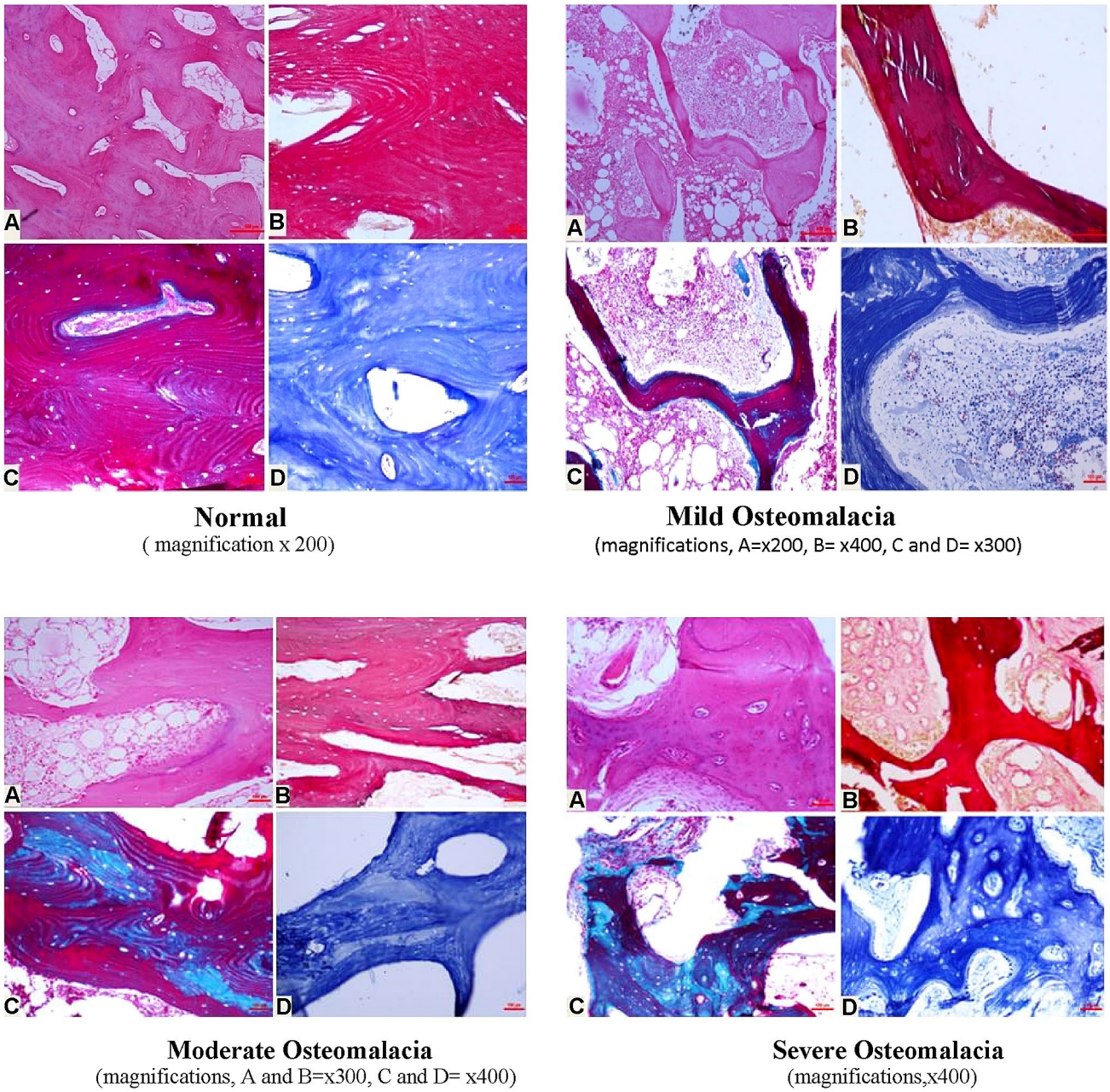

Fig. 1 The following photomicrographs of bone morphologies shown in Haematoxylin and eosin (**a**), Elastic Van Gieson (**b**), Masson' trichrome (**c**) and Solochrome cyanine (**d**) staining

Conclusion

Based on our study findings, we can say that in most of osteoporotic hip fracture patients, osteomalacia can coexist. Bone histopathology is gold standard to determine the presence of osteomalacia but is impractical especially if we are looking to screen the patient or if patient does not suffer from fracture. Biochemical findings may not give true picture of the disease so there is need to identify a biomarker or panel of markers that may correlate well with osteomalacia so that clinicians can screen, diagnose and provide adequate treatment of osteomalacia well in time before major fracture occurs.

Table 3 Correlation of biochemical markers and histopathology in 41 patients

Variables	No. of patients	Histopathology		*p* value
		Normal	Osteomalacia	
Serum calcium				
Normal/high	23 (56.1%)	8 (19.5%)	15 (36.6%)	0.291
Low	18 (43.9%)	3 (7.3%)	15 (36.6%)	
Serum phosphorus				
Normal/high	33 (80.5%)	9 (21.8%)	24 (58.5%)	1.000
Low	8 (19.5%)	2 (4.9%)	6 (14.6%)	
Serum ALP[a]				
Normal	21 (51.2%)	3 (7.3%)	18 (43.9%)	0.063
High	20 (48.8%)	8 (19.5%)	12 (29.3%)	
Corrected calcium				
Normal/high	23 (56.1%)	7 (17.1%)	16 (39.0%)	0.726
Low	18 (43.9%)	4 (9.7%)	14 (34.2%)	
Serum vitamin D				
Normal/high	22 (53.7%)	10 (24.4%)	12 (29.3%)	0.004
Low	19 (46.3%)	1 (2.4%)	18 (43.9%)	
Ca × P product				
Normal/high	26 (63.4%)	8 (19.5%)	18 (43.9%)	0.716
Low	15 (36.6%)	3 (7.3%)	12 (29.3%)	

[a]Alkaline phosphate, significant p value < 0.05

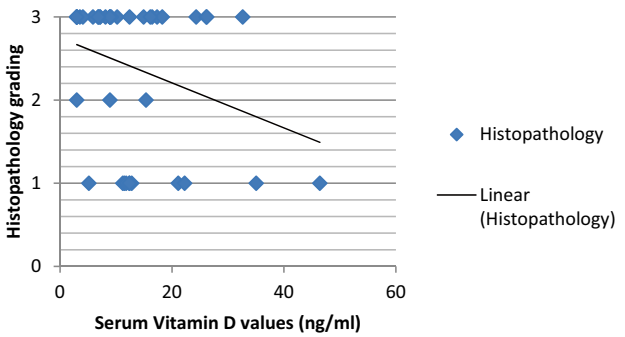

Fig. 2 Correlation between serum vitamin D values and histopathology grading (1—Normal, 2—mild, 3—moderate and severe)

Funding None.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

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

References

1. Parfitt, A. M. (1996). Osteomalacia and related disorders. In V. L. Avioli & S. M. Krane (Eds.), *Metabolic Bone Disease and Clinically Related Disorders* (3rd ed., pp. 327–386). New York: Academic Press.
2. Holick, M. F. (2007). Vitamin D deficiency. *New England Journal of Medicine, 357,* 266–281.
3. Rao, D. S. (1998). Role of vitamin D and calcium nutrition in bone health in India. In A. Mithal, D. S. Rao, & M. Zaidi (Eds.), *Metabolic Bone Disorders* (pp. 71–75). Lucknow: Hindustani Book Depot.
4. Malhotra, N., & Mithal, A. (2008). Osteoporosis in Indians. *Indian Journal of Medical Research, 127,* 263–268.
5. Goswami, R., Gupta, N., Goswami, D., Marwaha, R. K., Tandon, N., & Kochupillai, N. (2000). Prevalence and significance of low 25 hydroxyvitamin D concentrations in healthy subjects in Delhi. *American Journal of Clinical Nutrition, 72,* 472–475.
6. Harinarayan, C. V. (2005). Prevalence of vitamin D insufficiency in postmenopausal south Indian women. *Osteoporosis International, 16,* 397–402.
7. Khadgawat, R., Brar, K. S., Gahlot, M., Yadav, K. S., Malhotra, R., & Gupta, N. (2010). High prevalence of Vitamin D deficiency in Asian-Indian patients with fragility hip fracture: A Pilot Study. *Journal Association Physicians India, 58,* 539–542.
8. Mithal, A., & Kaur, P. (2012). Osteoporosis in Asia: A call to action. *Current Osteoporosis Reports, 10,* 245–247.
9. Schattner, A. (2018). The burden of hip fractures—why aren't we better at prevention? *QJM: An International Journal of Medicine, 111*(11), 765–767.
10. Tucker, G. S., Middha, V. P., Sural, A., & Sagreiya, K. (1988). Incidence of osteomalacia in fractures of the proximal end of femur. *Injury, 19,* 89–92.
11. Hordon, L. D., & Peacock, M. (1990). Osteomalacia and osteoporosis in femoral neck fracture. *Bone Mineral, 11,* 247–259.
12. Reginato, A. J., & Coquia, J. A. (2003). Musculoskeletal manifestations of osteomalacia and rickets. *Best Practice & Research: Clinical Rheumatology, 17,* 1063–1080.
13. Peacey, S. R. (2004). Routine biochemistry in suspected vitamin D deficiency. *Journal of the Royal Society of Medicine, 97,* 322–325.
14. Arnala, I., Kyrolak, K., Kroger, K., & Alhava, E. M. (1997). Analysis of 245 consecutive hip fracture patients with special reference to bone metabolism. *AnnChirGynaecol, 86,* 343–347.
15. Nampei, A., & Hashimoto, J. (2009). Bone fracture and the healing mechanisms. Metabolic bone disease and skeletal healing. *Clinical Calcium, 19,* 648–652.
16. Sanders, K. M., Scott, D., & Ebeling, P. R. (2014). Vitamin D deficiency and its role in muscle-bone interactions in the elderly. *Current Osteoporosis Reports, 12,* 74–81.
17. Bouillon, R. (2006). Vitamin D: From photosynthesis, metabolism, and action to clinical applications. In L. J. DeGroot & J. L. Jameson (Eds.), *Endocrinology* (5th ed., pp. 1435–1463). Philadelphia PA: Elsevier Saunders.
18. Berry, J. L., Davies, M., & Mee, A. P. (2002). Vitamin D metabolism, rickets, and osteomalacia. *Seminars in Musculoskeletal Radiology, 6,* 173–182.

19. Negri, A. L., Bogado, C. E., & Zanchetta, J. R. (2004). Bone densitometry in a patient with hypophosphatemic osteomalacia. *Journal of Bone and Mineral Metabolism, 22,* 514–517.
20. El-Desouki, M. I., Othman, S. M., & Fouda, M. A. (2004). Bone mineral density and bone scintigraphy in adult Saudi female patients with osteomalacia. *Saudi Medical Journal, 25,* 355–358.
21. Riaz, S., Alam, M., & Umer, M. (2006). Frequency of osteomalacia in elderly patients with hip fractures. *JPMA, 56,* 273.
22. Robinson, C. M., McQueen, M. M., Wheelwright, E. F., Gardner, D. L., & Salter, D. M. (1992). Changing prevalence of osteomalacia in hip fractures in southeast Scotland over a 20-year period. *Injury, 23,* 300–302.
23. Dawson-Hughes, B., Heaney, R. P., Holick, M. F., Lips, P., Meunier, P. J., & Vieth, R. (2005). Estimates of optimal vitamin D status. *Osteoporosis International, 16,* 713–716.
24. Cooper, C., & Barker, D. J. (1995). Risk factors for hip fracture. *New England Journal of Medicine, 332*(12), 814–815.
25. Nieves, J. W., Barrett-Connor, E., Siris, E. S., Zion, M., Barlas, S., & Chen, Y. T. (2008). Calcium and vitamin D intake influence bone mass, but not short-term fracture risk, in Caucasian postmenopausal women from the National Osteoporosis Risk Assessment (NORA) study. *Osteoporosis International, 19*(5), 673–679.
26. Qaseem, A., Forciea, M. A., McLean, R. M., Denberg, T. D., & Clinical Guidelines Committee of the American College of Physicians. (2017). Treatment of low bone density or osteoporosis to prevent fractures in men and women: A clinical practice guideline update from the american college of physicians. *Annals of Internal Medicine., 166*(11), 818–839.
27. Suresh, E., Pazianas, M., & Abrahamsen, B. (2014). Safety issues with bisphosphonates therapy for osteoporosis. *Rheumatology, 53*(1), 19–31.
28. Holick, M. F., Binkley, N. C., Bischoff- Ferrari, H. A., Gordon, C. M., Hanley, D. A., Heaney, R. P., et al. (2011). Evaluation, treatment and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology & Metabolism, 96,* 1911–1930.
29. Bhambri, R., Naik, V., Malhotra, N., Taneja, S., Rastogi, S., Ravishanker, U., & Mithal, A. (2006). Changes in bone mineral density following treatment of osteomalacia. *Journal of Clinical Densitometry, 9,* 120–127.
30. Priemel, M., von Domarus, C., Klatte, T. O., Kessler, S., Schlie, J., Meier, S., et al. (2010). Bone mineralization defects and vitamin D deficiency: Histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. *Journal of Bone and Mineral Research, 25,* 305–312.