Vertebral Fractures and Bone Mineral Density in Patients With Idiopathic Hypoparathyroidism on Long-Term Follow-Up

Himika Chawla,[1] Soma Saha,[1] Devasenathipathy Kandasamy,[2] Raju Sharma,[2] Vishnubhatla Sreenivas,[3] and Ravinder Goswami[1]

Departments of [1]Endocrinology and Metabolism, [2]Radiodiagnosis, and [3]Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Context: Bone mineral density (BMD) is increased in idiopathic hypoparathyroidism (IH). Parathyroid hormone (PTH) deficiency, hypocalcemic seizures, and anticonvulsants could compromise skeletal health in IH.

Objective: We assessed vertebral fractures (VFs) and related factors in IH and change in BMD during follow-up.

Design: VFs were assessed by morphometry. BMD was assessed by dual-energy X-ray absorptiometery at the lumbar spine, hip, and forearm. Change in BMD was assessed in a subset after a 10-year follow-up.

Setting: The endocrine clinic of All India Institute of Medical Sciences, New Delhi, India.

Subjects: Included were 104 patients with IH and 64 healthy controls. Hypocalcemia, hyperphosphatemia, normal kidney function, and low serum PTH levels were used to diagnose IH.

Results: VFs were seen in 18.3% of patients with IH and 4.7% of controls (odds ratio, 4.54; 95% confidence interval, 1.28 to 16.04). Use of anticonvulsants and menopause were significantly associated ($P < 0.05$) with VF. Mean BMD at lumbar spine and hip were higher by 21.4% and 8.6%, respectively, in IH than in controls ($P < 0.001$), respectively. BMD significantly increased during follow-up at all sites. Change in BMD correlated with maintenance of the serum calcium/phosphorus ratio during follow-up.

Conclusions: Despite increased BMD, prevalence of vertebral-fractures is greater in patients with IH, especially in postmenopausal women and those on anticonvulsant therapy. (***J Clin Endocrinol Metab* 102: 251–258, 2017**)

Patients with hypoparathyroidism demonstrate interesting skeletal manifestations (1). In our earlier study, bone mineral density (BMD) was increased at lumbar spine and hip but not at the forearm region in idiopathic hypoparathyroidism (IH) (2). Interestingly, quantitative computed tomography scan and histomorphometry of iliac crest biopsies have shown compromised bone microarchitecture, including increased cortical and trabecular width and reduced cortical porosity in hypoparathyroidism (1, 3, 4). The consequences of increased BMD and altered bone microarchitecture on skeletal health and vertebral fractures (VFs) are not known in IH because these fractures are often clinically silent (5). There is only one study where VFs were reported in 10 of 16 postmenopausal patients with postsurgical hypoparathyroidism (6). However, prevalence of VF was not increased in the Danish registry of hypoparathyroidism (7, 8). Lack of information on VF could be because of the rarity of patients with IH. Underbjerg *et al.* (7) observed only 47 cases of IH in the national registry of Denmark during 1977 to 2012. We

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received 23 September 2016. Accepted 3 November 2016.
First Published Online 4 November 2016

Abbreviations: BMD, bone mineral density; BMI, body mass index; DXA, dual-energy X-ray absorptiometery; IH, idiopathic hypoparathyroidism; iPTH, intact parathyroid hormone; PTH, parathyroid hormone; VF, vertebral fracture.

have been following patients with IH since 1998 to understand its etiopathogenesis and unique clinical features, including changes in BMD (9–17). Here, we report (a) the prevalence of VF in IH and associated risk factors, including duration of illness, history of seizures, use of anticonvulsants, presence of cataract, long-term calcemic and phosphatemic control, and menstrual status; and (b) change in BMD in patients with IH after a decade of oral calcium and vitamin D (1-α-hydroxyvitamin D and cholecalciferol) therapy.

Subjects and Methods

Subjects included 104 patients with IH attending endocrine clinics of the All India Institute of Medical Sciences, New Delhi, India, during 2014 to 2016. Pregnant, lactating women, patients on prolonged glucocorticoid therapy, and those with spine deformities were excluded. Patients < 12 years of age were also excluded for ethical reasons related to radiation exposure. Patients with postsurgical hypoparathyroidism were not part of the cohort of IH on long-term follow-up. Several patients with IH included in this study have participated in our earlier studies, including assessment of BMD in 2005 (2, 9–17). The diagnosis of IH was based on tetany, seizures, intracranial calcification, cataract, hypocalcemia, hyperphosphatemia, normal kidney function, and low serum intact parathyroid hormone (iPTH). None of the patients in the study had features of autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, and serum cortisol and adrenocorticotropic hormone (ACTH) were normal in the patients. Interferon-α autoantibody was positive in 1 of the 95 patients, and calcium-sensing receptor (CaSR) autoantibodies were positive in 12 out of 72 (16.7%) patients tested (14). None of the patients had mutation of the *CASR* and *PTH* genes (15, 16). Ten of the 104 patients had R110W mutation of the *GCM2* gene (17). All patients were advised to take a daily dose of 4 tablets of calcium carbonate (each tablet containing 500 mg of elemental calcium and 250 IU of cholecalciferol) and 0.5 to 3.0 μg of 1-alpha-hydroxyvitamin D and to undergo regular monitoring of serum total calcium, inorganic phosphorus, urinary calcium excretion, and abdominal ultrasound for nephrolithiasis/calcinosis. The therapy was adjusted with the aim to maintain serum calcium of 8.0 to 8.5 mg/dL.

A predesigned proforma was used to record duration of illness since onset of hypocalcemic symptoms, use of anticonvulsants, associated endocrinopathies, menstrual status, and symptoms of VF, such as backache, spinal tenderness, and deformities. Patients were also asked about history of fractures at any site in the past, which were confirmed on imaging by the treating physician. To understand the association of VF with serum total calcium and inorganic phosphorus maintained during follow-up, the average of these biochemical parameters from enrollment until the current study were recorded for all the patients. The mean number of measurements available was 23 ± 11 per patient.

Assessment of BMD and fractures

Patients were called in the fasting state for the assessment of BMD and radiograph of the spine for VF. BMD was measured by dual-energy X-ray absorptiometery (DXA) (Discovery A 84023; Hologic Inc., Marlborough, MA) at the lumbar spine (L1-4, anteroposterior), left hip, and nondominant forearm as per the guidelines of the International Society for Clinical Densitometry (18). The precision was measured by testing BMD 3 times in 15 study subjects using the International Society for Clinical Densitometry precision assessment tool (19). The coefficient of variation at the lumbar spine and hip was 1.3% and 1.5%, with the

Table 1. Clinical Characteristics, BMD at Various Sites, and Prevalence of VFs in Patients With IH and Controls

Parameters	IH (n = 104)	Controls (n = 64)	*P*	*P*[a]
Age, y	37.2 ± 1.45	37.53 ± 1.59	0.90	—
M:F (n)	56:48	39:25	0.37	—
BMI, kg/m^2	24.0 ± 4.63	25.9 ± 4.27	<0.01	—
Serum calcium, mg/dL	7.0 ± 1.31	9.1 ± 0.39	<0.001	—
Serum inorganic phosphorus, mg/dL	5.5 ± 1.15	3.7 ± 0.74	<0.001	—
Serum alkaline phosphatase, IU/L	214.2 ± 78.43	206.2 ± 62.0	0.49	—
Serum iPTH, pg/mL	8.2 ± 8.13	63.8 ± 26.11	<0.001	—
Median (IQR)	5.5 (3.1–11.1)	56.8 (43.5–86)		
Serum 25(OH) D, ng/mL	33.9 ± 19.76	10.7 ± 6.7	<0.001	—
BMD, g/cm^2				
L1-4 AP spine	1.183 ± 0.206	0.974 ± 0.122	<0.001	<0.001
Femoral neck	0.893 ± 0.174	0.790 ± 0.123	<0.001	<0.001
Trochanter	0.734 ± 0.123	0.667 ± 0.089	<0.001	<0.001
Total hip	1.005 ± 0.151	0.925 ± 0.121	<0.001	<0.001
Ultradistal forearm	0.421 ± 0.072	0.441 ± 0.071	0.08	0.30
Mid-forearm	0.593 ± 0.083	0.619 ± 0.072	0.04	0.08
Proximal forearm	0.717 ± 0.089	0.722 ± 0.091	0.71	0.93
Total forearm	0.565 ± 0.132	0.594 ± 0.070	0.10	0.20
History of fractures at any site in the past	17 (18.3)	5 (7.8)	0.11	—
Vertebral fractures				
At least 1 vertebra	19 (18.3)	3 (4.7)	0.01	—
Multiple vertebrae	11 (10.6)	0 (0)	<0.01	—

Values are mean ± SD, n (%), or as otherwise indicated.

Abbreviations: 25(OH) D, 25-hydroxyvitamin D; AP, anteroposterior; F, female; IQR, interquartile range; M, male.

[a]Values adjusted for age, sex, and BMI.

least significant change being 0.046, 0.038, and 0.019 g/cm^2 at the spine, hip, and forearm, respectively. Fractured vertebrae were excluded from the BMD analysis. The T and *z* scores were not analyzed because of the lack of reference of BMD for a large Asian Indian population. Patients with prominent syndesmophytes, deformities, and ligamentous calcification of the spine on radiograph were excluded from BMD analysis (20).

Presence of VF was assessed by SpineAnalyzer quantitative vertebral morphometry software (Optasia Medical, Cheadle, UK) (21). Lateral thoracic and lumbar spine radiographs centered at T7 and L3 vertebrae were acquired in quiet breathing and breath holding after expiration, respectively, with a tube-receptor distance of 100 cm. For the vertebral morphometry, radiographs were imported in digital imaging and communications in medicine (DICOM) image format, and the center of the T4-L4 vertebrae were marked manually. The software outlined each vertebra using 95 points, connected by line segments which were manually checked and adjusted for accurate marking. The wedge and biconcave deformity was calculated from the ratios of anterior and posterior heights of the vertebrae. The crush deformity was calculated using ratios of anterior, mid, and posterior heights of the adjacent vertebrae. VFs were graded based on the degree of deformity (grade 1: 20% to 24.9%; grade 2: 25% to 39.9%; and grade 3: ≥40%). A radiologist blinded to the results of vertebral morphometry analysis also assessed the radiographs for VF using the Genant method (22). Patients with VF were reexamined for chest expansion and ratio of upper and lower body segments.

Controls were family members of patients with IH consenting for spine radiographs and DXA. The exclusion criteria for controls were the same as that for IH. None of the controls had hypoparathyroidism, and their mean iPTH, serum total calcium, and inorganic phosphorus were 63.8 ± 26.11 pg/mL, 9.1 ± 0.39 mg/dL, and 3.7 ± 0.74 mg/dL, respectively.

Change in BMD in IH during follow-up on calcium and vitamin D therapy

Change in BMD was assessed in 27 of the 47 patients with IH who participated in our earlier study on BMD in the year 2005 and were available for follow-up during the current study (2). Nine of these 27 patients were <30 years of age in 2005. A stratified analysis was also performed after excluding these 9 patients because they might not have achieved peak bone mass in 2005. The initial DXA in 2005 was performed on QDR4500 A (Hologic Inc.), which was replaced with Discovery A 84023 in 2009 because of its shorter scan time. During replacement, the 2 DXA systems were cross-calibrated by performing 10 phantom scans with repositioning before and after hardware change, and the difference in mean BMD was only 0.9% (18).

The study was carried out in accordance with the tenets of the Declaration of Helsinki after approval from the Ethics Committee of the All India Institute of Medical Sciences, New Delhi. Written informed consent was obtained from all the patients and controls.

Biochemical measurement

The serum total calcium, inorganic phosphorus, and alkaline phosphatase were measured on Hitachi 917 (Roche, Mannheim, Germany) (normal range, 8.1 to 10.4 mg/dL, 2.5 to 4.5 mg/dL, and 80 to 240 IU/L, respectively). The intra- and interassay coefficients of variation were 3.5% to 5.0%. Serum iPTH was measured by IRMA until 2006 (DiaSorin, Inc., Stillwater, MN) (minimum detection limit, 1.7 pg/mL; normal range, 13 to 54 pg/mL) and subsequently by chemiluminescence (Elecsys-2010; Roche) (minimum detection limit, 1.2 pg/mL; normal range, 15 to 65 pg/mL). Serum 25-hydroxyvitamin D was measured by chemiluminiscence (LAISON; DiaSorin, Inc.) with coefficient of variation of 2.9% to 5.5%.

Statistical analysis

Data are presented as mean and standard deviation, median with interquartile range, and frequencies in percentage. Differences in the BMD between IH and control groups were assessed with adjustment for differences in age, sex, and BMI. Parametric and nonparametric tests were used as appropriate. Multiple regression analysis was used to determine variables associated with increased BMD and VF in patients with IH. A 2-tailed *P* value <0.05 was considered significant. All the analyses were done with Stata 12.1 (StataCorp LP, College Station, TX).

Results

There were 110 patients with IH who attended the endocrine outdoor patient clinic during the study period. Six of them were excluded (pregnancy: n =1, lactation: n = 1,

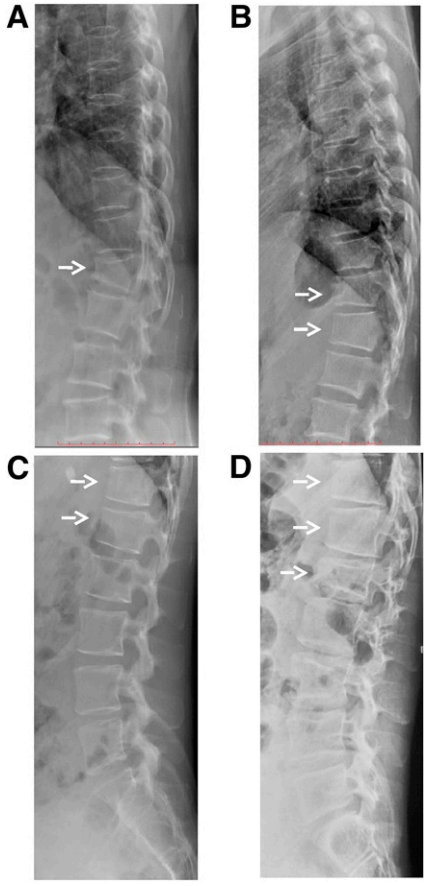

Figure 1. Radiographs representative of patients with idiopathic hypoparathyroidism and vertebral fractures, as shown by arrows, at different levels: (A) L1; (B) T11 and T12; (C) T12 and L1; and (D) T11, T12, and L1.

glucocorticoid use for rheumatoid arthritis: n = 1, spine deformity: n = 2, and age <12 years: n = 1). Finally, 104 patients were analyzed. The male to female ratio, mean age, body mass index (BMI), and duration of disease were 56:48, 37.2 ± 1.45 years, 24.0 ± 4.63 kg/m^2, and 15.1 ± 6.61 years, respectively. Intracranial calcification and cataract were present in 72.1% and 44.2% of the patients, respectively. The baseline mean serum calcium, inorganic phosphorus, and iPTH were 5.4 ±1.0 mg/dL, 7.0 ± 1.52 mg/dL, and 8.2 ± 8.13 pg/mL (median, 5.5; interquartile range, 3.1 to 11.1 pg/mL), respectively. Eighty patients had history of seizures, and 53 of them received different types of anticonvulsant given alone or in combination: phenytoin (25%), valproate (36.7%), carbamazepine (20.0%), levetiracetam (18.3%), and phenobarbitone (3.3%). Thirteen patients had coexistent primary hypothyroidism, and 3 had celiac disease. They were on L-thyroxine and a gluten-free diet, respectively (13). Besides, 3 patients had other autoimmune diseases (alopecia areata: n = 1, alopecia totalis: n = 1, and vitiligo: n = 1). The alopecia in both the patients improved spontaneously during follow-up. Nonautoimmune comorbidities in the present cohort of IH included mental retardation (n = 5), mild hearing loss (n = 3), type 2 diabetes mellitus (n = 1), coronary artery disease (n = 1), hyperprolactinemia (n = 1), fibrous dysplasia (n = 1), history of surgery for acoustic neuroma (n = 1), acyanotic tetralogy of Fallot (n = 1), atrial septal defect (n = 1), and Takayasu arteritis (n = 1). None of these patients were on steroid or any other therapy affecting bone mineral homeostasis. Fifteen of the 48 female patients with IH were postmenopausal. None of them had premature ovarian failure.

Sixty-five family members of patients with IH consented to participate as controls. One of them had spine deformity and was excluded. The male to female ratio and mean age (39:25 and 37.5 ± 1.59 years, respectively) were comparable with those of the IH group. However, mean BMI of controls (25.9 ± 4.27 kg/m^2) was higher than that of the IH group ($P < 0.01$).

Pattern of BMD in IH

Table 1 shows the mean BMD at total lumbar spine, hip, and forearm in study subjects. The mean BMD at the lumbar spine and hip was higher by 21.4% and 8.6%, respectively, in patients with IH compared with controls ($P < 0.001$ for both). The differences in BMD were significant even after adjustment for age, sex, and BMI (Table 1). The mean BMD at the forearm, including total, ultradistal, mid, and proximal regions, were comparable between IH and controls. On univariate analysis, BMD at the lumbar spine showed positive association with age ($P = 0.03$) and inverse association with serum iPTH ($P = 0.02$), but no significant association with sex, BMI, menstrual status (analyzed only for women with IH), duration of illness, use of anticonvulsants, and duration of anticonvulsant use. In the regression model for predictors of lumbar spine BMD, calcium-phosphorus product at presentation, mean serum total calcium, and calcium/phosphorus ratio during follow-up were also included because of their borderline significance ($P = 0.1$, $P = 0.08$, and $P = 0.10$, respectively) and clinical relevance. Serum iPTH emerged as the

Table 2. Distribution of Site and Severity of VFs in Patients With IH

Patient No.	Total No. of VFs	Site of VF	Severity of VF	
			No. of Grade 1 VFs	No. of Grade 2 VFs
1	5	T5-9	1	4
2	1	T6	0	1
3	2	T6, T12	2	0
4	2	T12, L2	1	1
5	2	T6, T8	1	1
6	1	T12	1	0
7	2	T11, T12	1	1
8	1	T12	1	0
9	2	T8, L1	1	1
10	1	T11	1	0
11	1	L1	0	1
12	1	T12	0	1
13	2	T12, L1	2	0
14	1	T10	1	0
15	3	T8, L1, L2	1	2
16	2	T6, T7	2	0
17	4	T10, T11, T12, L1	3	1
18	5	T5, T6, T7, T11, T12	3	2
19	1	T11	0	1

The wedge and biconcave deformity was calculated from the ratios of anterior and posterior heights of the vertebrae.

Abbreviations: Grade 1, degree of deformity 20% to 24.9%; Grade 2, degree of deformity 25% to 39.9%.

Table 3. Clinical Characteristics of IH Patients With and Without VFs

Parameter	With VF (n = 19)	Without VF (n = 85)	*P*
Age, y	37.9 ± 15.27	37.1 ± 14.79	0.82
M:F (n)	7:12	44:41	0.37
BMI, kg/m^2	21.5 ± 3.97	20.9 ± 4.01	0.60
Age at onset of symptoms, y	20.7 ± 14.66	24.8 ± 13.52	0.24
Age at initial presentation, y	29.6 ± 12.07	31.2 ± 13.27	0.64
Duration of illness at initial presentation, y	9.2 ± 7.38	6.2 ± 5.97	0.06
Median (IQR)	7 (3–13)	4 (2–9)	
Current duration of illness, y	18 ± 10.8	14.3 ± 7.72	0.08
Basal ganglia calcification	17 (89.5)	58 (69)	0.07
Cataract	11 (61.1)	35 (42.2)	0.14
Seizures	16 (84.2)	54 (63.5)	0.08
Use of anticonvulsants	13 (68.4)	40 (47.1)	0.09
Duration of anticonvulsant use, y	10.9 ± 7.25	5.8 ± 4.29	<0.01
Hypothyroidism on L-thyroxine	2 (10.5)	11 (13.2)	0.75
Coexisting celiac disease	1 (5.3)	2 (2.3)	0.45
Postmenopausal patients in women with IH, n/N (%)	6/7 (85.7)	9/41 (21.9)	0.02
History of fractures at any site in the past	5 (26.3)	12 (14.1)	0.19
Serum total Ca at initial presentation, mg/dL	5.5 ± 1.09	5.4 ± 0.99	0.81
Serum PO4 at initial presentation, mg/dL	7.2 ± 1.35	7.0 ± 1.56	0.64
Ca-PO4 product at initial presentation	38.4 ± 7.42	37.2 ± 9.67	0.66
Ca/PO4 ratio at initial presentation	0.8 ± 0.25	0.82 ± 0.27	0.81
Serum ALP at initial presentation, IU	250 ± 148.9	243 ± 124.3	0.83
24-h urinary calcium excretion at initial presentation, mg/d	85.4 ± 55.69	78.9 ± 58.64	0.59
Serum iPTH at initial presentation, pg/mL	6.5 ± 7.69	8.5 ± 8.23	0.09
Median (IQR)	6.3 (3.5–9.9)	3.4 (1–11.15)	
Follow-up serum total Ca, mg/dL	7.2 ± 0.82	7.2 ± 0.82	0.94
Serum 25(OH)D, ng/mL	39.8 ± 22.77	32.8 ± 19.14	0.26
Serum PO4 during follow-up, mg/dL	5.8 ± 1.12	5.7 ± 0.88	0.67
Ca-PO4 product during follow-up	41.7 ± 4.75	41.2 ± 6.08	0.76
Ca/PO4 ratio during follow-up	1.29 ± 0.31	1.30 ± 0.29	0.95
BMD, g/cm^2			
L1-4 AP spine	1.152 ± 0.198	1.189 ± 0.208	0.48
Femoral neck	0.854 ± 0.159	0.902 ± 0.176	0.28
Trochanter	0.717 ± 0.110	0.737 ± 0.125	0.52
Total hip	0.991 ± 0.147	1.008 ± 0.152	0.65
Ultradistal forearm	0.396 ± 0.070	0.426 ± 0.72	0.10
Mid-forearm	0.571 ± 0.080	0.598 ± 0.083	0.20
Proximal forearm	0.707 ± 0.091	0.719 ± 0.091	0.59
Total forearm	0.555 ± 0.074	0.566 ± 0.142	0.73

Values are mean ± SD, n (%), or as otherwise indicated.

Abbreviations: 25(OH) D, 25-hydroxyvitamin D; ALP, alkaline phosphatase; AP, anteroposterior; F, female; IQR, interquartile range; M, male.

significant predictor of BMD at the lumbar spine (r^2 = 0.05, P = 0.02) and hip (r^2 = 0.16, $P < 0.001$).

Prevalence of VFs in IH

Nineteen patients (18.3%) with IH had VF, and multiple VFs were present in 11 of them (Fig. 1). Only 3 (4.7%) of the controls had VF, and none of them had multiple VFs. The prevalence of VF was significantly higher in IH than controls (odds ratio, 4.54; 95% confidence interval, 1.28 to 16.04; P = 0.01). Altogether, there were 39 VFs in 19 patients with IH. Of the 39 VFs, 29 could be identified by the radiologist by the Genant method.

Table 2 shows the distribution of VF in IH according to sites and severity. Altogether, there were 39 VFs in 19 patients with IH; of these, 23 were in the T10-L2 region, with the most common site being the T12 vertebra. Twenty-eight VFs in IH showed wedge deformity, and 10 had wedge deformity with crush and/or biconcave deformity. Crush deformity alone was observed in only 1 vertebra. Twelve of the 19 patients with VF had grade 2 deformity. Only 3 patients with VF (15.7%) had history of sudden onset backache or restriction of spinal movements, and upper to lower segment ratio was normal in all of them (0.97 ± 0.04). Patients with VF were advised spinal strengthening exercises.

Univariate and multivariate regression analysis for VFs in IH

Table 3 shows the potential factors determining susceptibility to VFs in IH. The mean age, BMI, duration of illness, frequency of cataract, intracranial calcification, hypothyroidism, and celiac disease were comparable in

Table 4. Change in BMD (grams per square centimeter) During Long-Term Follow-Up in 27 Patients With IH

Site	Year 2005	Year 2015	*P*
Total lumbar spine			
All 27 patients	1.079 ± 0.170	1.225 ± 0.169	< 0.001
Patients ≥30 y of age in 2005 (n = 18)	1.131 ± 0.116	1.235 ± 0.162	< 0.001
Total hip			
All 27 patients	0.969 ± 0.139	1.027 ± 0.167	0.02
Patients ≥30 y of age in 2005 (n = 18)	0.993 ± 0.124	1.015 ± 0.160	0.89
Total forearm			
All 27 patients	0.524 ± 0.087	0.582 ± 0.071	< 0.001
Patients ≥30 y of age in 2005 (n = 18)	0.560 ± 0.067	0.590 ± 0.075	< 0.001

Values are mean ± SD or as otherwise indicated.

patients with VF (n = 19) and without VF (n = 85). Similarly, there were no differences in the mean BMD at all sites, mean serum total calcium, inorganic phosphorus, calcium-phosphorus product and its ratio, and alkaline phosphatase at initial presentation and during follow-up in the 2 groups. History of seizures and use of anticonvulsants tended to be higher in IH patients with VF than in those without VF (84.2% *vs* 63.5% and 68.4% *vs* 47.1%; $P = 0.08$ and $P = 0.09$, respectively). The duration of anticonvulsant use was significantly longer in patients with VF compared with those without VF (10.9 ± 7.25 *vs* 5.8 ± 4.29 years, respectively; $P < 0.01$). There was no significant difference in the type of anticonvulsant therapy used between patients with and without VFs. On stratified analysis in women with IH, the prevalence of VF was significantly higher in postmenopausal women (6/15) than in menstruating women (1/33, $P = 0.002$). On stepwise regression, presence of VF in IH correlated with longer use of anticonvulsants (odds ratio, 1.15; 95% confidence interval, 1.05 to 1.25; $P = 0.03$), but not with other factors, including BMD at the lumbar spine. On similar regression analysis in women with IH, menopause was the most significant predictor (odds ratio, 20.7; 95% confidence interval, 2.2 to 194.8; $P = 0.008$).

Change in BMD over a decade of follow-up in IH

Table 4 shows the change in BMD in 27 patients with IH during 10 years of follow-up. The mean BMD significantly increased at all 3 regions, with the highest change at the lumbar spine followed by the forearm. On stratified analysis in subjects who were ≥30 years of age in 2005 (n = 18), BMD change was significant only at the lumbar spine and forearm. The change in BMD at the lumbar spine in IH correlated significantly with the average serum phosphorus and calcium phosphorus ratio during 10 years of follow-up ($r^2 = 0.16$ and $r^2 = 0.18$, $P = 0.04$ and $P = 0.03$, respectively).

Discussion

Parathyroid hormone (PTH) deficiency, hypocalcemic seizures, and anticonvulsants could compromise skeletal health in IH. The clinical impact of these factors on VFs in IH is not known. Recently, a position statement on management guidelines in hypoparathyroidism suggested assessment of fractures as an area of future research (23). The current study was carried out in a well-characterized cohort of patients with IH to assess the prevalence of VF and its association with factors unique to hypoparathyroidism, such as increased BMD, history of seizures, use of anticonvulsants, and calcium and phosphorus control during follow-up. This study also assessed change in BMD in IH and its related factors after a decade of follow-up.

In this study, patients with IH showed an increase in BMD by 21% at the lumbar spine and by 8% at the hip, with no significant change at the forearm. The importance of the PTH deficiency as the cause of increased BMD in IH was evident from the regression analysis showing an inverse relation of PTH with BMD. This also suggests that the physiologic resorptive action of PTH on bone is intact even in IH with low circulating PTH. The average calcium and phosphorus levels maintained by patients on long-term follow-up on oral calcium and vitamin D therapy showed no association with BMD.

Currently, there is no obvious reason to explain the site-related differences in BMD in IH. Differential increase in BMD might be related to the ratio of trabecular/cortical bone at different sites, which is highest in the spine, followed by the hip, and lowest at the forearm (24). The preferential increase in BMD at the trabecular bone–rich vertebrae in IH is unlikely to be explained by catabolic action of PTH alone. In the catabolic model (*i.e.*, hyperparathyroidism), there is a greater reduction in BMD at the forearm than at the lumbar spine (25). The expected reverse (*i.e.*, increase in BMD at the forearm in IH) was not observed in this study. On the other hand, in the anabolic model of PTH action as exemplified by low-dose intermittent PTH therapy in osteoporosis, BMD improves remarkably in the vertebrae rather than the forearm (26). Thus, the pattern of increased BMD at the spine in IH with subnormal circulating PTH resembles the anabolic model of PTH action.

Prospective assessment of BMD during follow-up provided further insights into factors contributing toward increased BMD in IH. The change in BMD was highest at the lumbar spine and correlated significantly with mean serum phosphorus over 10 years of follow-up. There is no previous study assessing long-term change in BMD and related factors in IH. However, the correlation of progressive increase in lumbar spine BMD with serum phosphorus is akin to our earlier observations in IH, where the presence and progression of intracranial calcification correlated with serum phosphorus and calcium/phosphorus ratio (10). Thus, altered PTH dynamics and hyperphosphatemia seem to be the important contributory factors for the increase in BMD in IH.

The increased BMD in IH might not translate into improved skeletal strength. This study showed that 18% of IH patients had VFs, with 58% of these being multiple VFs. Presence of most VFs in the T10-L2 region with wedge deformity indicated the role of flexion compression forces rather than falls in their occurrence. This was supported by the fact that all except 1 of the 19 patients with IH were not aware of VFs and diagnosed only during this study. History of sudden onset backache and VF after a fall was noticed after an episode of hypocalcemic seizure in only 1 patient. The distribution, grade, wedge deformity, and clinically asymptomatic nature of VF in IH are analogous to osteoporosis, where they are often detected on routine screening (5). Increased prevalence of VF in IH despite increased BMD could be related to their altered bone microarchitecture. Rubin *et al.* (27) demonstrated improved cortical porosity, number of Haversian canals, trabecular width, and connectivity on histomorphometric analysis of iliac-crest biopsies with PTH therapy in patients with hypoparathyroidism.

This study indicated longer use of anticonvulsants as the most significant determinant for VF in IH, with the risk increasing by 15% per year of anticonvulsant use. Interestingly, 40% of the VFs were in the T5-8 region. Similar fractures have been observed in patients with seizures and are related to violent muscle contractions during seizures and anticonvulsant-associated bone microarchitecture abnormalities (28–30). Among women with IH, menopause was the most important predictor of VF. The study by Mendonça *et al.* (6), reporting 63% prevalence of VF in postmenopausal women with surgical hypoparathyroidism, also supports the increased risk of VF in them. Patients with IH also tended to have high frequency of trauma-related fracture, especially in the upper extremity. Recently, Underbjerg *et al.* (7) reported a moderately increased risk of upper extremity fracture in patients with nonsurgical hypoparathyroidism.

The present study has some limitations. We could not assess bone microarchitectural changes because these facilities are not available at our institution. Further studies assessing microarchitectural abnormalities along with BMD and their interplay with VF would help understand the pathogenesis of VFs among patients with hypoparathyroidism more clearly.

Thus, a relevant proportion of patients with IH (18.3%) have VFs despite increased BMD at the lumbar spine. The increased BMD in IH correlates with subnormal serum PTH and hyperphosphatemia during long-term follow-up. Prolonged use of anticonvulsants and menopause are important associates of VF. Most VFs were clinically silent and were detected during this study. The high prevalence of VFs observed in IH is clinically important because these could result in spine deformities and impaired quality of life. Patients with IH should therefore be regularly screened for the presence of VF despite increased BMD, especially postmenopausal women and those on anticonvulsant therapy for hypocalcemic seizures, and regular spinal strengthening exercises should be advised to them. Efforts should be made to maintain a good calcemic control for withdrawal of anticonvulsants as early as possible (11).

Acknowledgments

The authors thank Mr Sushil Chugh, technician, for help in carrying out DXA on the study subjects.

Address all correspondence and requests for reprints to: Ravinder Goswami, MD, DM (Endocrinology), Department of Endocrinology and Metabolism, All India Institute of Medical Sciences, New Delhi 110029, India. E-mail: gosravinder@hotmail.com.

Disclosure Summary: The authors have nothing to disclose.

References

1. Silva BC, Rubin MR, Cusano NE, Bilezikian JP. Bone imaging in hypoparathyroidism [published online ahead of print August 30, 2016]. *Osteoporos Int*.
2. Laway BA, Goswami R, Singh N, Gupta N, Seith A. Pattern of bone mineral density in patients with sporadic idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)*. 2006;**64**(4):405–409.
3. Rubin MR, Dempster DW, Zhou H, Shane E, Nickolas T, Sliney J, Jr, Silverberg SJ, Bilezikian JP. Dynamic and structural properties of the skeleton in hypoparathyroidism. *J Bone Miner Res*. 2008; **23**(12): 2018–2024.
4. Cusano NE, Nishiyama KK, Zhang C, Rubin MR, Boutroy S, McMahon DJ, Guo XE, Bilezikian JP. Noninvasive assessment of skeletal microstructure and estimated bone strength in hypoparathyroidism. *J Bone Miner Res*. 2016;**31**(2):308–316.
5. Delmas PD, van de Langerijt L, Watts NB, Eastell R, Genant H, Grauer A, Cahall DL; IMPACT Study Group. Underdiagnosis of vertebral fractures is a worldwide problem: the IMPACT study. *J Bone Miner Res*. 2005;**20**:557–563.
6. Mendonça ML, Pereira FA, Nogueira-Barbosa MH, Monsignore LM, Teixeira SR, Watanabe PC, Maciel LM, de Paula FJ. Increased vertebral morphometric fracture in patients with postsurgical hypoparathyroidism despite normal bone mineral density. *BMC Endocr Disord*. 2013;**13**:1.
7. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. The epidemiology of nonsurgical hypoparathyroidism in Denmark:

a nationwide case finding study. *J Bone Miner Res*. 2015;**30**(9):1738–1744.
8. Underbjerg L, Sikjaer T, Mosekilde L, Rejnmark L. Postsurgical hypoparathyroidism–risk of fractures, psychiatric diseases, cancer, cataract, and infections. *J Bone Miner Res*. 2014;**29**(11):2504–2510.
9. Goswami R, Millo T, Mishra S, Das M, Kapoor M, Tomar N, Saha S, Roy TS, Sreenivas V. Expression of osteogenic molecules in the caudate nucleus and gray matter and their potential relevance for Basal Ganglia calcification in hypoparathyroidism. *J Clin Endocrinol Metab*. 2014;**99**(5):1741–1748.
10. Goswami R, Sharma R, Sreenivas V, Gupta N, Ganapathy A, Das S. Prevalence and progression of basal ganglia calcification and its pathogenic mechanism in patients with idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)*. 2012;**77**(2):200–206.
11. Modi S, Tripathi M, Saha S, Goswami R. Seizures in patients with idiopathic hypoparathyroidism: effect of antiepileptic drug withdrawal on recurrence of seizures and serum calcium control. *Eur J Endocrinol*. 2014;**170**(5):777–783.
12. Saha S, Gantyala SP, Aggarwal S, Sreenivas V, Tandon R, Goswami R. Long-term outcome of cataract surgery in patients with idiopathic hypoparathyroidism and its relationship with their calcemic status [published online ahead of print July 27, 2016]. *J Bone Miner Metab*.
13. Saha S, Saini S, Makharia GK, Datta Gupta S, Goswami R. Prevalence of coeliac disease in idiopathic hypoparathyroidism and effect of gluten-free diet on calcaemic control. *Clin Endocrinol (Oxf)*. 2016;**84**(4):578–586.
14. Tomar N, Gupta N, Goswami R. Calcium-sensing receptor autoantibodies and idiopathic hypoparathyroidism. *J Clin Endocrinol Metab*. 2013;**98**(9):3884–3891.
15. Sarin R, Tomar N, Ray D, Gupta N, Sharma YD, Goswami R. Absence of pathogenic calcium sensing receptor mutations in sporadic idiopathic hypoparathyroidism. *Clin Endocrinol (Oxf)*. 2006;**65**(3):359–363.
16. Goswami R, Mohapatra T, Gupta N, Rani R, Tomar N, Dikshit A, Sharma RK. Parathyroid hormone gene polymorphism and sporadic idiopathic hypoparathyroidism. *J Clin Endocrinol Metab*. 2004;**89**(10):4840–4845.
17. Tomar N, Bora H, Singh R, Gupta N, Kaur P, Chauhan SS, Sharma YD, Goswami R. Presence and significance of a R110W mutation in the DNA-binding domain of GCM2 gene in patients with isolated hypoparathyroidism and their family members. *Eur J Endocrinol*. 2010;**162**(2):407–421.
18. ISCD. 2015 ISCD official positions – adult. Available at: http://www.iscd.org/official-positions/2015-iscd-official-positions-adult. Accessed 24 June 2016.
19. ISCD. Calculators. Available at: www.iscd.org/resources/calculators. Accessed 4 July 2016.
20. Goswami R, Ray D, Sharma R, Tomar N, Gupta R, Gupta N, Sreenivas V. Presence of spondyloarthropathy and its clinical profile in patients with hypoparathyroidism. *Clin Endocrinol (Oxf)*. 2008;**68**(2):258–263.
21. Marwaha RK, Tandon N, Gupta Y, Bhadra K, Narang A, Mani K, Mithal A, Kukreja S. The prevalence of and risk factors for radiographic vertebral fractures in older Indian women and men: Delhi Vertebral Osteoporosis Study (DeVOS). *Arch Osteoporos*. 2012;**7**:201–207.
22. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. *J Bone Miner Res*. 1993;**8**(9):1137–1148.
23. Brandi ML, Bilezikian JP, Shoback D, Bouillon R, Clarke BL, Thakker RV, Khan AA, Potts JT, Jr. Management of hypoparathyroidism: summary statement and guidelines. *J Clin Endocrinol Metab*. 2016;**101**(6):2273–2283.
24. Bonnic SL. Skeletal anatomy in desitometry. In: Bonnic SL, ed. *Bone Densitometry in Clinical Practice Application and Interpretation*. Totowa, NJ: Humana Press; 2004:29–67.
25. Castellano E, Attanasio R, Gianotti L, Cesario F, Tassone F, Borretta G. Forearm DXA increases the rate of patients with asymptomatic primary hyperparathyroidism meeting surgical criteria. *J Clin Endocrinol Metab*. 2016;**101**(7):2728–2732.
26. Shen L, Xie X, Su Y, Luo C, Zhang C, Zeng B. Parathyroid hormone versus bisphosphonate treatment on bone mineral density in osteoporosis therapy: a meta-analysis of randomized controlled trials. *PLoS One*. 2011;**6**(10):e26267.
27. Rubin MR, Dempster DW, Sliney J, Jr, Zhou H, Nickolas TL, Stein EM, Dworakowski E, Dellabadia M, Ives R, McMahon DJ, Zhang C, Silverberg SJ, Shane E, Cremers S, Bilezikian JP. PTH(1-84) administration reverses abnormal bone-remodeling dynamics and structure in hypoparathyroidism. *J Bone Miner Res*. 2011;**26**(11):2727–2736.
28. El Asri AC, Akhaddar A, Baallal H, El Mostarchid B, Boulahroud O, Belfquih H, Dao I, Naama O, Gazzaz M, Boucetta M. Hypocalcemic seizure in adult: rare cause of lumbar fracture. *Clin Neurol Neurosurg*. 2012;**114**(6):738–740.
29. Nicholas JM, Ridsdale L, Richardson MP, Grieve AP, Gulliford MC. Fracture risk with use of liver enzyme inducing antiepileptic drugs in people with active epilepsy: cohort study using the general practice research database. *Seizure*. 2013;**22**(1):37–42.
30. Vestergaard P, Rejnmark L, Mosekilde L. Fracture risk associated with use of antiepileptic drugs. *Epilepsia*. 2004;**45**(11):1330–1337.