

ORIGINAL ARTICLE

Osteoporosis: An ignored complication of CVIDSafa Baris¹, Ahmet Ozen², Hulya Ercan², Elif Karakoc-Aydiner¹, Hasret Cagan¹, Cevdet Ozdemir¹, Metin Barlan³, Nerin N. Bahceciler¹ & Isil B. Barlan¹¹Division of Pediatric Allergy and Immunology, Marmara University, Istanbul, Turkey; ²Division of Pediatric Allergy and Immunology, Yeditepe University, Istanbul, Turkey; ³Division of Radiology, Florence Nightingale Hospital, Istanbul, Turkey**To cite this article:** Baris S, Ozen A, Ercan H, Karakoc-Aydiner E, Cagan H, Ozdemir C, Barlan M, Bahceciler NN, Barlan IB. Osteoporosis: An ignored complication of CVID. *Pediatr Allergy Immunol* 2011; Doi: 10.1111/j.1399-3038.2011.01187.x.**Keywords**

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Abstract**Background:** Multiple factors in common variable immunodeficiency (CVID) might interfere with optimal growth and maturation and potentially compromise bone health.**Methods:** We aimed to evaluate bone mineral density (BMD) of patients with CVID using dual energy X-ray absorptiometry (DEXA) and investigate risk factors associated with decreased bone density.**Results:** Twenty-two patients were included (M: 16, F: 6) with a mean age of 15.6 ± 9.0 yr. DEXA revealed osteopenia in 6/22 (27.3%) and osteoporosis in 9/22 (40.9%) at lumbar spine and osteopenia in 7/19 (37%) and osteoporosis in 3/19 (16%) at femoral neck sites. The age of subjects with osteoporosis was significantly higher than those without (21.6 ± 8.0 vs. 9.0 ± 5.7 yr; $p < 0.0001$). BMD z-scores were significantly lower in patients with bronchiectasis compared with those without ($p = 0.03$). Patients with osteoporosis at femoral neck site had lower forced expiratory volume in 1 s (FEV_1) ($p = 0.024$), FEV_1 /forced vital capacity (FVC) ($p < 0.0001$), PEF ($p = 0.008$), and FEF 25–75 ($p = 0.013$) values compared with the patients with normal BMD z-scores. Low serum 25(OH) vitamin D levels were detected in 13/22 patients and low dietary calcium intake in 17/22 patients. BMD z-scores at femoral neck were lower in patients with low B-cell percentage ($p = 0.03$). BMD z-score at lumbar spine was correlated with folate ($r = +0.63$, $p = 0.004$) and serum immunoglobulin G levels ($r = +0.430$, $p = 0.04$).**Conclusion:** Osteoporosis appeared as an emerging health problem of patients with CVID, the risk increasing with older age and poorer lung function. Nutritional, biochemical, and immunologic factors appeared to take part in decreased BMD. Insight into the mechanisms of osteoporosis in CVID is crucial to develop preventive strategies.

Common variable immunodeficiency (CVID) is a primary antibody deficiency affecting people at any age, but with peaks in the first and third decades. Most patients are identified because they have recurrent infections with encapsulated bacterial pathogens. However, the disease has been variably associated with a diverse array of neoplastic, granulomatous, and autoimmune diseases such as sprue-like syndrome, gastric atrophy, hemolytic or pernicious anemia, thyroid abnormalities, and arthritis (1). Systemic complications can occur despite treatment, including bronchiectasis, gastric carcinoma, lymphoreticular malignancy, amyloidosis, and non-caseating granulomas of the lungs, spleen, skin, and liver. High rates of secondary complications justify periodic assessment of CVID patients with screening tests to detect these disorders in a timely manner.

The prognosis of treated patients with CVID is reasonably good, unless severe autoimmune disease or malignancy develops. As the life expectancy continues to increase with modern therapeutic modalities, long-term quality of life issues become an ever-important concern. Most of the patients experience chronic lower airway infections resulting in bronchiectasis that leads to restriction of pulmonary function, decreased physical activity, and frequent hospitalization (1). Recurrent infections, chronic inflammation, chronic nutritional deficits, and associated gastrointestinal abnormalities may pose threats to optimal growth and maturation. All these pathological events known to compromise bone health might potentially lead to osteoporosis. However, bone mineral content of patients with CVID has not been addressed so far.

The peak bone mass is formed during the later adolescence period and acts as a storage for rest of life. Multiple factors contribute to building normal bone mass architecture. Well-balanced nutrition is important, as is adequate amount of calcium and vitamin D. Also age, weight, height, growth hormone, thyroid, sex hormones, as well as regular physical activity are other related factors (2, 3). Various systemic disorders such as chronic malnutrition, celiac disease, chronic liver disease, and several endocrinological disorders as well as chronic obstructive lung diseases are associated with osteoporosis. It has been shown that as many as 60% of adult patients with obstructive airways disease (4) and one-third of children with cystic fibrosis (CF) have decreased bone mass (5), with an increase in the risk of osteoporosis as the airway obstruction worsens (6). The low bone mineral density (BMD) in individuals with these diseases is multifactorial (7). Several mechanisms have been suggested to explain the relationship between obstructive airway diseases and increased risk of fracture or osteoporosis, including lack of physical activity, low body mass index, a decreased exposure to sunlight, decreased testosterone levels, hypercapnia, and chronic inflammation.

We hypothesized that various pathological events experienced by patients with CVID over many years in childhood, a critical period for healthy bone accrual, might lead to defects in bone mineralization. In this study, we aimed to investigate BMD of patients with CVID with a specific emphasis on the roles of nutritional status and pulmonary function as well as relevant immunologic and biochemical markers.

Material and methods

Study population and anthropometric measures

The study group included 22 patients with CVID followed at Pediatric Allergy and Immunology outpatient clinic of Marmara University Hospital. The study was approved by the Ethical Committee of the Marmara University. CVID was diagnosed using standard criteria (8), including low level of serum IgG, IgA, and/or IgM more than 2 SD from the normal mean, absent or poor response to vaccines, and exclusion of other defined causes of hypogammaglobulinemia. Anthropometric measures included body weight and height, which were then transformed into standard deviation scores (SDS) using data for Turkish children (9). Pubertal development was evaluated according to the method of Tanner (10) and bone age according to Greulich and Pyle (11).

Assessment of laboratory and radiology findings

Serum calcium, phosphate, and total alkaline phosphatase (ALP) levels were measured with BM/Hitachi automatic analyzer. 25(OH) vitamin D and parathyroid hormone (PTH) levels were measured by radio assay kits (Incstar Corp., Stillwater, MN, USA). Serum folate and vitamin B12 were measured with chemiluminescence method using an Architect B12 Reagent kit and Architect Folate Reagent kit by Immulyte

2000 (Bio DPC, Los Angeles CA, USA) analyzer. The serum biochemical parameters were compared with normal reference values (12). Serum levels of immunoglobulin isotypes (IgG, IgA, IgM) and subclasses of IgG were analyzed by nephelometric method in the biochemistry laboratory of Marmara University Hospital (Dade Behring BN2, Germany). Lymphocyte subsets from peripheral blood were performed by means of fluorescent-activated cell sorting (FACS) with the following cluster of differentiation (CD) antigens: total T cells (CD3+), helper T cells (CD3+/CD4+), cytotoxic T cells (CD3+/CD8+), and B cells (CD19+, CD20+). The diagnosis of chronic lung disease was based on characteristic high-resolution computed tomography (HRCT) findings. The normal value for 25 (OH) vitamin D was accepted as > 50 nm (13).

Daily calcium and caloric intake, medication usage and fracture history

Dietary calcium and caloric intake was calculated based on a 3-day nutritional diary. Adequate dietary calcium intake was accepted as >800 mg for pre-pubertal children and >1200 mg for pubertal children (14). Also, cumulative inhaled steroid dosages and history of bone fracture were recorded.

Pulmonary function testing

PFTs were performed by means of maximal forced expiratory volume curves (Zan Flowhandy II; Zan Messgerate GmbH, Oberthulba, Germany). The best of three successful maneuvers was recorded and expressed as the percentage of predicted values for gender, age, and height as forced expiratory volume in 1 s (FEV₁), forced vital capacity (FVC), forced mid-expiratory flow rate (FEF 25–75%), and peak expiratory flow rate (PEF).

Assessment of BMD

Areal BMD of the lumbar spine and femoral neck was measured with dual energy X-ray absorptiometry (DEXA; Hologic QDR 4500A, Waltham, MA, USA) (g/cm²), and z-scores of aBMD were calculated. Age- and sex-based z-scores of BMDs indicating osteopenia or osteoporosis risks were calculated. Z-score values >−1 SD below the mean were considered as normal, between −1 SD and −2 SD below the mean as osteopenia, and <−2 SD as osteoporosis. Reference values belong to 345 (176 girls and 169 boys) healthy Turkish children aged between 2 and 18 yr (15) and for adults obtained from another population of 466 (347 women and 119 men) aged between 20 and 79 yr (16).

Statistics analyses

Data were described as frequencies, median, and means with standard deviations (SD) unless otherwise indicated. Data were analyzed using the Student's *t*-tests, analysis of variance (ANOVA) with Tukey honestly significant differences (HSD)

for continuous variables, and chi-squared analysis for categorical variables. All analyses were performed using Statistical Package for the Social Sciences (SPSS) program (Version 16.0; Chicago, IL, USA) using default settings. $p < 0.05$ was set as the level of statistical significance.

Results

Twenty-two patients (M: 16, F: 6) with a mean age of 14.8 ± 9.0 yr (range: 4–38 yr) were enrolled into the study. The mean follow-up period was 4.4 ± 4.1 yr. Demographic data, BMD z -scores, biochemical, immunologic parameters, and PFTs are presented in Tables 1–3.

Assessment of growth and puberty

Mean body weight and height were 41.57 ± 18.0 kg and 142.1 ± 26.0 cm, respectively. Height and weight of the subjects were <3 percentile in 8/22 (37%) and 8/22 (37%), respectively. Among those patients, bronchiectasis was identified as the major cause of failure to thrive in seven and growth hormone deficiency in one patient. DEXA z -score at lumbar site was positively correlated with height SDS ($r = +0.83$, $p < 0.0001$) and weight SDS values ($r = +0.86$, $p < 0.0001$). Mean bone age was 15.2 ± 9.3 yr, and six patients had low bone age with respect to chronologic age (more than 1.5 yr below chronologic age). All patients had normal pubertal status.

Assessment of BMD

DEXA revealed osteopenia in 6/22 (27.3%) and osteoporosis in 9/22 (40.9%) at lumbar spine and osteopenia in 7/19 (37%) and osteoporosis in 3/19 (16%) at femoral neck sites. BMD z -scores at lumbar site was negatively correlated with age ($r = -0.59$, $p = 0.007$). The subjects with osteoporosis were significantly older than those without (21.6 ± 8.0 vs. 9.0 ± 5.7 yr; $p < 0.0001$) (Fig. 1).

Assessment of laboratory and radiologic findings

While all the patients had folate levels within normal limits, BMD z -score had a significant correlation with serum folate levels ($r = +0.66$, $p = 0.004$ at femoral neck, $r = +0.63$, $p = 0.004$ at lumbar spine sites, respectively) (Fig. 2a,b). Serum folate levels of patients with osteoporosis were lower than those with normal BMD (5.7 ± 1.6 vs. 9.8 ± 3.4 ng/ml, $p = 0.01$). There were no significant correlations between BMD z -score and other biochemical parameters, including calcium, phosphate, vitamin D, ALP, PTH, and vitamin B12 levels. Serum 25(OH) vitamin D levels (mean = 35.89 ± 27.21 nm) were below the lower limit of reference in 13 patients. No significant association was detected between BMD z -scores and serum 25(OH) vitamin D level. ALP and PTH were above the reference ranges in 5 and 4 of the patients, respectively. All the other biochemical parameters were within normal limits for ages. Nine of the patients (41%) had

Table 1 Demographic data, z -scores of BMD, pulmonary function tests, and bronchiectasis of patients with CVID

Patients	Age (yr)/ gender	Consanguinity	Age of onset (months)	Age at diagnosis (months)	z -score at femoral neck	z -score at lumbar spine	Lung function (FEV ₁ %)	Bronchiectasis
1	24/M	+	46	120	-2.0	-2.3	51	+
2	4/M	+	6	24	-	-1.8	-	-
3	38/M	+	168	420	-1.8	-4.1	91	-
4	10/M	+	38	44	-0.8	-1.5	89	-
5	18/F	-	9	72	-1.8	-2.7	56	+
6	10/F	+	36	100	0.5	1.2	56	-
7	4/M	-	4	29	-	-1.6	-	-
8	10/M	-	60	96	-0.4	-2.3	124	+
9	18/M	-	36	135	-1.3	-2.0	106	-
10	16/M	+	84	118	-1.4	-2.8	38	+
11	15/F	-	24	108	0.0	-1.8	118	-
12	8/M	+	48	60	2.1	1.3	97	-
13	10/M	-	26	41	0.5	0.8	90	-
14	23/M	-	120	250	-2.3	-2.5	18	+
15	10/F	-	4	100	-2.0	-1.8	91	+
16	9/M	+	7	96	-1.1	-1.5	-	-
17	27/F	-	72	216	-2.0	-2.1	19	+
18	28/F	-	12	72	-1.2	-3.1	45	-
19	5/M	+	14	28	-1.7	-0.6	-	-
20	19/M	+	25	38	-0.4	-0.2	106	-
21	15/M	+	6	96	1.2	0.1	98	-
22	6/M	+	3	18	-0.5	-0.7	88	-

CVID, common variable immunodeficiency; BMD, bone mineral density.

Table 2 Biochemical parameters, daily calcium and energy intake, and inhaled steroid usage of patients with CVID

Patients	Folate levels (ng/ml)	Vitamin B12 (pg/ml)	25(OH)D3 vitamin (nm)	Serum Ca (mg/dl)	Serum P (mg/dl)	Daily energy intake (Kcal)	Daily calcium intake (mg)	Inhaled steroid usage (g)*
1	7.0	393	65	9.5	4.1	2771	1223	0.72
2	4.7	1028	10	10.4	4.5	1502	753	–
3	5.9	363	16	9.4	3.3	2987	858	–
4	8.8	234	18	9.7	4.0	1027	670	0.11
5	5.3	446	39	8.9	4.6	1680	495	3.6
6	13.6	483	14	9.3	4.4	1128	570	0.9
7	7.4	1240	20	8.7	4.8	1133	1076	–
8	11.0	385	45	9.2	4.4	1298	750	0.18
9	4.0	368	–	9.7	4.1	1814	900	1.44
10	6.8	346	10	9.4	4.7	2165	670	2.16
11	6.6	221	43	10.5	4.6	1743	373	–
12	15.6	565	53	9.1	4.2	2001	661	–
13	7.0	533	43	9.8	4.7	3109	1016	0.14
14	7.6	425	21	9.6	3.1	1094	300	0.92
15	4.8	339	122	10.0	4.1	1120	428	0.14
16	7.9	489	34	9.3	4.3	1354	876	–
17	5.0	850	–	7.0	4.5	1469	200	1.8
18	5.0	819	52	9.0	4.7	2713	664	1.88
19	7.3	399	55	9.2	4.4	785	565	0.28
20	10.0	220	12	9.9	4.8	1794	961	0.36
21	6.1	332	52	9.4	3.1	2008	503	1.2
22	7.7	341	57	9.8	4.5	2180	859	–

CVID, common variable immunodeficiency. *Cumulative dose.

Table 3 Immunological findings of patients with CVID

Patients	Percentage of B cell (%)*	Serum IgG (mg/dl)	Serum IgA (mg/dl)	Serum IgM (mg/dl)
1	11	700	23	95
2	14	431	24	83
3	28	522	64	24
4	17	767	54	60
5	5	716	28	89
6	21	1150	27	36
7	8	173	22	17
8	15	890	53	36
9	11	880	23	55
10	12	154	29	81
11	20	750	46	28
12	24	879	6	57
13	9	587	39	28
14	5	596	42	32
15	20	538	23	41
16	4	572	55	86
17	6	258	20	18
18	14	240	25	67
19	24	565	32	16
20	12	790	25	51
21	23	430	25	18
22	20	679	21	68

CVID, common variable immunodeficiency. *% of lymphocytes.

abnormal HRCT findings; seven with bronchiectasis, one with nodule, and one with fibrotic band. BMD *z*-scores at lumbar spine and femoral neck were significantly lower in patients with bronchiectasis compared with those without ($p = 0.03$, $p = 0.03$, respectively; Table 4). Patients with lower B-cell percentage ($n = 6$) had lower BMD *z*-scores compared with those with normal B cells ($n = 16$) at femoral neck (-0.49 ± 1.20 vs. -1.80 ± 0.34 ; $p = 0.03$) and at lumbar spine (-1.15 ± 1.52 vs. -2.26 ± 0.56 ; $p = 0.02$). Serum IgG levels were positively correlated with *z*-scores of lumbar spine ($r = +0.430$, $p = 0.04$).

Daily calcium and caloric intake, medication usage and fracture history

The calculated dietary calcium intakes were below the recommended amounts in 17 of 22 patients (mean = 698.9 ± 267.7 mg/day). BMD *z*-scores were not related to dietary calcium intake or cumulative dose of inhaled steroids. However, daily calcium intake was significantly lower in patients with osteoporosis compared with those without (309 ± 114 mg/day in patients with osteoporosis, 717 ± 164 mg/day in osteopenia and 688 ± 219 mg/day in those with normal BMD *z*-score, $p = 0.02$). Patients with low caloric intake ($n = 17$) had lower femur *z*-scores than those with adequate intakes (0.23 ± 1.43 vs. -1.02 ± 1.01 , $p = 0.04$). Five patients had a history of fractures in the upper extremities with minor trauma, four of which had osteoporosis at lumbar spine site (mean *z*-scores:

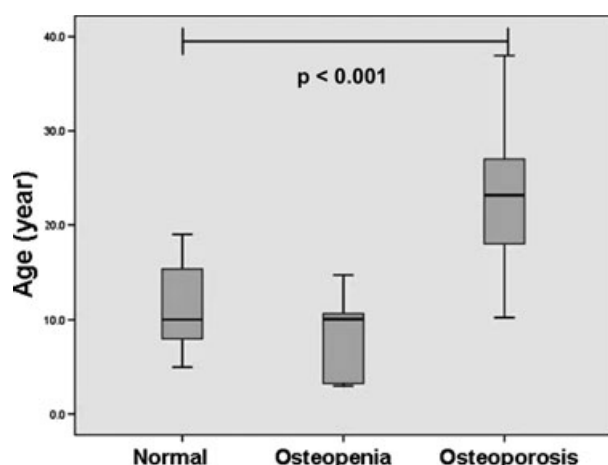


Figure 1 Distribution of age of patients according to presence of osteoporosis at lumbar spine.

-2.0 ± 0.9). Of note, all of those patients with fractures were older than 15 yr of age.

Pulmonary function testing

Half of the patients had decreased PFTs (Table 1); seven of them (32%) with severe impaired lung function ($FEV_1 < 60\%$ of predicted). BMD z-scores at femoral neck site demonstrated a significant correlation with FEV_1 , PEF, and FVC values (Fig. 3). Patients with osteoporosis at femoral neck site had lower FEV_1 ($p = 0.024$), FEV_1/FVC ($p < 0.0001$), PEF ($p = 0.008$), and FEF 25–75 ($p = 0.013$) values compared with the patients with normal BMD z-scores (Fig. 4). All PFT parameters were significantly lower in patients with bronchiectasis compared with those with normal HRCT findings (Table 4).

Discussion

In this cohort of 22 patients with CVID, osteoporosis appeared as an emerging health problem among the adolescents or young adults who grew up with the unfavorable consequences of CVID. Four patients older than 15 experienced bone fractures because of osteoporosis. Risk factors associated with low BMD values included older age, impaired

Table 4 Laboratory findings of patients with and without bronchiectasis ($n = 7$ vs. $n = 15$)

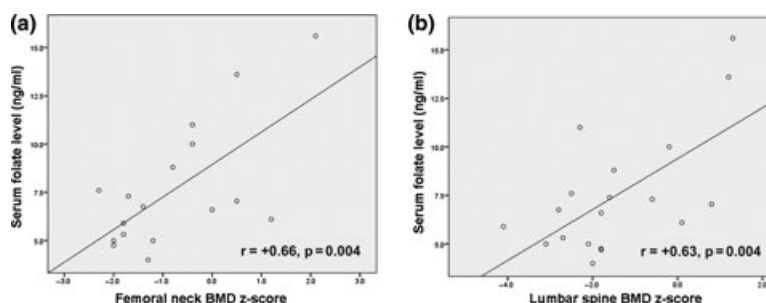
Parameters	HRCT	Mean $\pm$ SD	p-value
$FEV_1\%$ predicted	Normal	90.2 ± 19.4	0.04
	Bronchiectasis	56.7 ± 38.7	
FVC % predicted	Normal	82.2 ± 22.0	0.08
	Bronchiectasis	57.0 ± 29.7	
FEV_1/FVC % predicted	Normal	105.7 ± 9.6	0.06
	Bronchiectasis	81.8 ± 32.2	
PEF % predicted	Normal	84.7 ± 19.6	0.01
	Bronchiectasis	46.4 ± 34.8	
PEF 25–75% predicted	Normal	98.7 ± 39.1	0.04
	Bronchiectasis	49.7 ± 45.9	
Dietary calcium intake (mg/day)	Normal	806.2 ± 184.6	0.09
	Bronchiectasis	580.8 ± 342.4	
25(OH) vitamin D (nm)	Normal	33.1 ± 19.3	0.38
	Bronchiectasis	47.4 ± 43.9	
Folate (ng/ml)	Normal	7.4 ± 3.2	0.59
	Bronchiectasis	8.4 ± 5.1	
Lumbar spine z-score	Normal	-1.1 ± 1.6	0.03
	Bronchiectasis	-2.3 ± 0.3	
Femoral neck z-score	Normal	-0.37 ± 1.3	0.03
	Bronchiectasis	-1.7 ± 0.6	

FEV_1 , forced expiratory volume in 1 s; FVC, forced vital capacity; HRCT, high-resolution computed tomography; PEF, peak expiratory flow rate.

pulmonary function testing, low serum folate and 25 (OH) vitamin D levels, presence of bronchiectasis, low dietary calcium and caloric intake, lower B-cell count and serum IgG levels.

DEXA revealed low BMD in 15/22 of patients at lumbar spine and 10/19 at femoral neck site. It appeared that osteoporosis and bone fracture were primarily a disease of patients who are older than 15 yr of age, suggesting the role of prolonged exposure to detrimental health conditions. Likewise, the more severe the CVID phenotype it is more likely that the patient has lower BMD. Impact of poor respiratory function on osteoporosis has been demonstrated in children with CF as well non-CF bronchiectasis (17). Several mechanisms were suggested to explain the susceptibility of those patients for defective bone mineralization including decreased muscle mass, short stature, delayed puberty, malnutrition, physical inactivity, steroid usage, recurrent lung infections causing

Figure 2 Association between serum folate levels and bone mineral density (BMD) z-scores at (a) Femoral neck, (b) Lumbar spine.



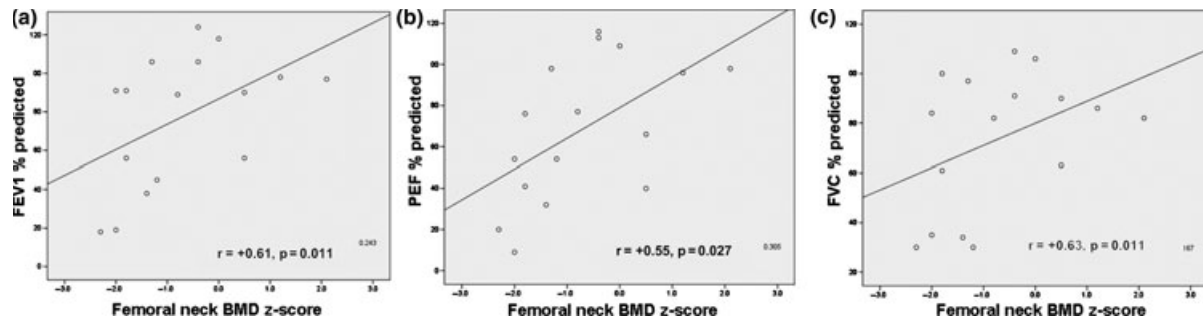


Figure 3 Association between pulmonary function and bone mineral density (BMD) z-scores at femoral neck sites. (a) Forced expiratory volume in 1 s (FEV₁), (b) peak expiratory flow rate (PEF), (c)

forced vital capacity (FVC). Values are presented as percent predicted.

chronic hypoxia, and chronic inflammation (17, 18). In our study, most of the patients had one or more of those risk factors, placing them at risk for osteoporosis; all had recurrent infections causing chronic inflammation, nine (41%) abnormal HRCT findings, seven (32%) severe impaired lung function (FEV₁ < 60% of predicted), eight (36%) growth retardation, 17 (77%) inadequate dietary calcium intake, and 13 (59%) vitamin D deficiency. Obviously, more effort should be invested on the evaluation of those conditions for the prevention of the sequelae and thus improvement of the overall health of these patients.

Decreased BMD was associated with older age, bronchiectasis, impaired lung function, inadequate dietary calcium and caloric intake, lower serum vitamin D level, and lower B-cell count. Meanwhile, DEXA z-score was correlated positively with height and weight SDS values, serum folate level, serum IgG level, and negatively with age. Studies on post-menopausal women suggested an important role of folates on BMD, and its deficiency through hyperhomocystinuria was associated with bone loss (19, 20). However, the association between folates and BMD has not been investigated in patients with CVID so far. It seems plausible that each of the

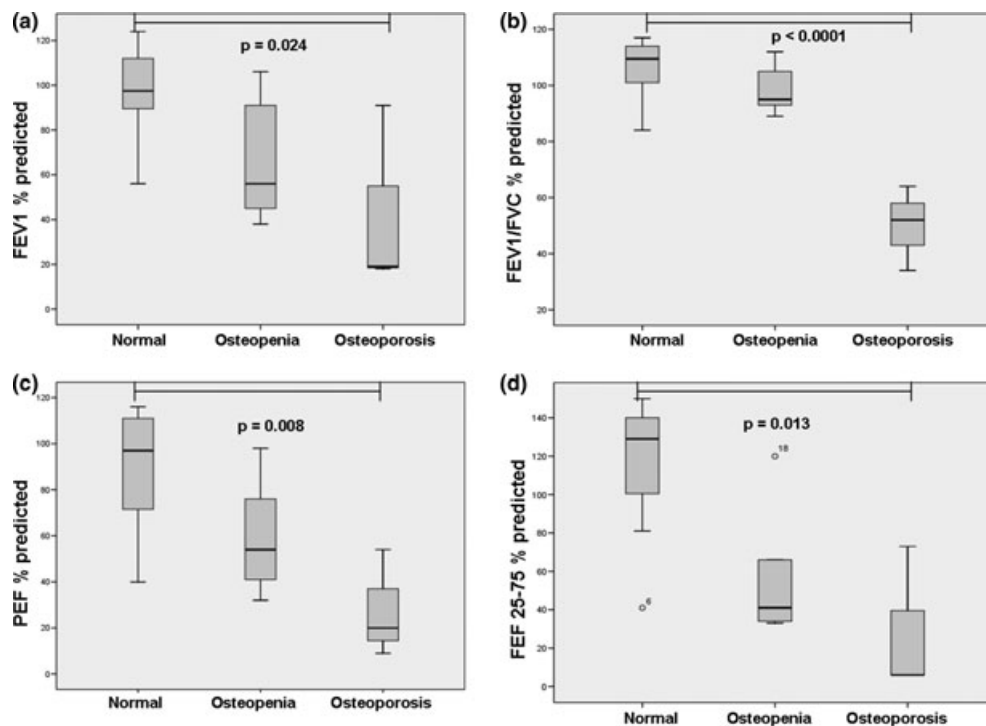


Figure 4 Pulmonary function tests of patients according to bone mineral density (BMD) z-scores at femoral neck site. (a) Forced expiratory volume in 1 s (FEV₁), (b) FEV₁/forced vital capacity (FVC),

(c) peak expiratory flow rate (PEF), (d) forced mid-expiratory flow (FEF) rate 25–75. Values are presented as percent predicted.

parameters identified as a risk for defective bone mineralization, individually or collectively might have contributed to osteoporosis. Although their putative roles as causative mechanisms might be a possible explanation, given that CVID is frequently associated with non-infectious involvement of multiple organ systems and the detection of decreased bone density at unexpectedly high rates, it is more likely that osteoporosis is one of the consequences of immunologic dysregulation associated with the disease.

A number of cell surface receptors, cytokines, and signaling pathways serve a critical role both in the immune and skeletal systems. It has been demonstrated that lymphocytes and a number of key cytokines take part in the regulation of osteoclastogenesis and osteoblast function which recently lead to a term as osteoimmunology (21). In this regard, a disturbance in bone metabolism has been described in certain immunologic disorders including human immunodeficiency virus (HIV) infection and CVID (21), which was suggested to be related with enhanced TNF activity (22, 23). Some of the patients with CVID were shown to have markedly elevated serum levels of the proinflammatory cytokines IL-6 and TNF- α , which have been related with enhanced bone resorption (3, 18, 22). Osteoprotegerin (OPG) which is a member of the TNF receptor superfamily, inhibitor of receptor activator of NF- κ B ligand, and identified as a candidate factor in the paracrine signaling between osteoblasts and osteoclasts which was found to be elevated in both of these situations (24). The study conducted by Shead et al. (25) demonstrated significant correlations between osteoclast formation and serum TNF α , OPG, osteocalcin, and type I collagen cross-linked N-telopeptide and concluded that the systemic response to

infection is associated with increased bone resorptive activity in patients with CF. In an experimental study, B cells were shown as source of OPG and that B-cell deficient mice had reduced bone mass, which could be reversed by adoptive transfer of B cells (26). Likewise, the association of BMD with low B-cell count and IgG level in our study might implicate an immunologic basis for the osteoporosis observed in our patients with CVID.

A primary limitation to our study is the cross-sectional design and relatively small sample size to delineate the independent risk factors. Our study is entirely an association study among a heterogeneous group of patients with CVID. The determinants of BMD, role of preventive measures on the outcome, and immunologic basis for the situation needs to be elucidated by larger studies particularly of longitudinal design.

In conclusion, this study demonstrated that a significant proportion of patients with CVID eventually develop osteoporosis, with bone fractures and compromise the quality of life. It is intriguing that lower serum folate and total IgG level as well as B-cell count were related to decreased BMD. Further studies are needed to identify the exact mechanisms by which CVID leads to decreased bone density and to determine whether earlier intervention and screening programs could help prevent development of osteoporosis. A verification of our study on a different patient cohort from a different genetic background is warranted.

Conflict of interest

Authors declare no conflict of interest.

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