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Bone Metabolism Alterations in Patients with Common Variable Immune Deficiency: A Retrospective Cohort Study

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ABSTRACT

Objective: Common variable immunodeficiency (CVID) is a relatively frequent primary immunodeficiency disorder characterized by impaired B cell differentiation with hypogammaglobulinemia in the European Society for Immunodeficiencies (ESID) registry system. Increased inflammatory cytokines, prolonged and/or recurrent infections, gastrointestinal complications, and anti-inflammatory medications are risk factors for diminished bone mineral density (BMD) in CVID patients.

Materials and Methods: The study group included 32 patients with CVID (19 males and 13 females; mean age: 37.33 ± 13.70 years, 40.6% female), who had been followed up on a regular basis for a period of four years. The patients were categorized into two groups according to their BMD: low BMD and normal BMD.

Results: Seventeen patients (8 females and 9 males) had normal BMD (mean age 34.94 ± 11.41 years, 47.1% female) and fifteen patients (5 females and 10 males) had low BMD (mean age 40.03 ± 15.87 years, 33.3% female). In the low BMD group, three patients had osteoporosis and 12 patients had osteopenia. Univariate regression analysis revealed that lymphopenia (odds ratio, OR:6.562, 95% confidence interval, CI: 1.095-39.324, p=0.039) was significantly associated with low BMD. Multivariate regression analysis showed that higher alkaline phosphatase (ALP) levels (OR:1.017, 95% CI 1.001-1.033, p=0.041), lymphopenia (OR:11.028, 95% CI 1.326-91.709, p=0.026), and lower folic acid levels (OR:1.284, 95% CI 1.007-1.637, p=0.043) were also independent predictors for low BMD.

Conclusion: Even with some limitations such as the small number for the study population, a single center experience, and a cross-sectional design, we recommend that clinical immunologists should be alert for diminished BMD in CVID patients, especially those with low folic acid and high ALP levels and lymphopenia.

Keywords: Bone mineral density, common variable immune deficiency, hypogammaglobulinemia, lymphopenia

INTRODUCTION

Common variable immunodeficiency (CVID) is a relatively frequent primary immunodeficiency disorder characterized by impaired B cell differentiation with hypogammaglobulinemia and diminished antibody responses in the European Society for Immunodeficiencies (ESID) registry system (1). CVID patients have an increased susceptibility to infection, particularly of the respiratory tract (2), in addition to autoimmunity (3), malignancy (4), infectious and non-infectious inflammatory disorders of the gastrointestinal tract (5), and lymphoproliferation (6). Because of this heterogeneity, a diagnostic delay of six to seven years is inevitable (7).

Osteoporosis is characterized by low bone mass, micro architectural disruption, and skeletal fragility, and is mainly is age-related. It has been detected during the course of many chronic inflammatory diseases including rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, inflammatory bowel disease, and chronic obstructive pulmonary disease (8). Though corticosteroid treatment is a common characteristic in these disorders, bone loss seems to be related to chronic inflammation rather than the corticosteroid effect. Increased inflammatory cytokines, prolonged and/or recurrent infections, gastrointestinal complications such as malabsorption or malnutrition, chronic pulmonary disorders, and steroids or anti-inflammatory medications are the most cited risk factors for diminished bone mineral density (BMD) in CVID patients.

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Among the above factors, one must especially consider infections in CVID patients in terms of a reduction in BMD. Recurrent and chronic infections cause increased proinflammatory cytokines, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha, and result in an imbalance in bone metabolism (9). These proinflammatory cytokines are mainly secreted from the immune system cells and these cell-derived regulatory signals stimulate osteoblasts for the maturation of osteoclasts. In addition, increased hospitalization and immobilization may also cause bone demineralization in CVID patients. Further, chronic diarrhea from CVID may cause malabsorption that affects the calcium and vitamin D metabolism and accordingly bone health negatively. In addition, a recent study has shown that the gut microbiota (GM) play an important role in bone formation (10).

Immunoglobulin G (IgG) replacement therapy is still the cornerstone of CVID management and alters the course of recurrent infections. However, IgG replacement therapy may not change the progress of many comorbid problems despite the considerable degree of control of infections it provides. Patients with CVID usually pass away because of comorbidities and/or complications other than infections. Early detection of possible or probable comorbid disorders and setting up effective management for them may provide better quality of life and a longer lifespan for these patients.

In this study, we aimed to investigate BMD in patients with CVID as low BMD is a possible overlooked complication of CVID, and we aimed to identify possible risk factors associated with low BMD.

MATERIALS and METHODS

The study group included 32 patients with CVID, who had been followed up on a regular basis for a period of four years. The study protocol was approved by the ethics committee of the university (Date: October 20, 2017; approval number: 2017/043). Informed consent was obtained from the study participants. Diagnosis of CVID was made according to the updated diagnostic criteria of the ESID (11).

Demographic and clinical data including, gender, age, current and preceding symptoms, diagnostic delay, detailed family history, body mass density (BMD), smoking status, and all other necessary information were retrieved from the individual medical files, and all been recorded at the first visit of the patients. Smoking at least one cigarette regularly every day for at least six months is consireded as being a current smoker. The results of initial immunological workup and other diagnostic investigations to determine an exact diagnosis and concurrent complications and/or disorders had also been recorded. Further, the details noted during regular visits were also reviewed and retrieved from the files.

Complete blood count (Abbott Cell Dyn 3700 series, Sheath reagent) was performed, and the calcium, phosphorus, serum parathyroid hormone (PTH), alkaline phosphatase, albumin (Abbott Architect c16000 chemistry system), 25(OH) vitamin D, folic acid and vitamin B12 (Siemens Advia 2400 Clinical Chemistry System, colorimetric method) levels were measured.

Quantitative determination of serum immunoglobulins (IgG, IgM, IgA, and IgE) was made by means of particle-enhanced immunonephelometry using the Siemens BN II/ BN ProSpec system. Peripheral blood lymphocyte subsets were measured with the BD FACSCanto II 8-color configuration flow cytometer system using fluorescently labeled antibodies.

Spirometric measurements were obtained using a common protocol with the nSpire ZAN 100 spirometer. Although additional tests may be needed if one or more of the curves are unacceptable, three maneuvers were performed. The forced expiratory volume in one second (FEV1), the FEV1/FVC (forced vital capacity) ratio, peak expiratory flow (PEF), and mean expiratory flow between 25%-75% of the predicted values for similar age, sex, race and height were recorded.

BMD was measured for femoral and lumbar spine by using the General Electric Lunar DPX Bone Densitometer. Z scores values > -1 SD (Standard Deviation) below the mean were considered normal, while values between -1 SD and -2.5 SD below the mean were considered osteopenia, and values ≤ -2.5 SD as osteoporosis for premenopausal women and also men younger than 50 years (12,13). For post-menopausal women and men older than 50 years, the T-score was used (13). The patients were categorized into two groups as low BMD and normal BMD according to the BMD value. Both the patients with osteopenia and those with osteoporosis were included in the low BMD group.

Statistical analysis was performed with the IBM SPSS Statistics Version 22 software package. Normally

distributed parameters were presented as mean ± standard deviation and data that were not normally distributed were expressed as median (interquartile range: minimum–maximum). Descriptive data were presented as frequencies and percentages and compared using a Chi-square test. Comparisons between baseline characteristics were performed by independent Student t, Mann-Whitney rank-sum, Fisher exact, or Chi-square tests, as appropriate. Binomial logistic regression analysis was performed to determine independent predictors for the presence of low BMD. While Pearson correlation analysis was used for normally distributed parameters, Spearman rank correlation analysis was used for non-parametric variables.

RESULTS

Characteristics of the Patients

Thirty-two patients (19 males and 13 females) who had sufficient data in their personal medical files and agreed to participate in the study were included in the study (mean age: 37.33 ± 13.70 years, 40.6% female). The mean diagnostic delay was 102 months (range 0 to 360 months). Ten patients (33.3%) had parental consanguinity while an additional 10 patients (33.3%) expressed that "their parents had no consanguinity but they were from the same village." In this study, 18 of 32 patients (56.25%) had low FEV1 and were using an inhaled corticosteroid treatment with a cumulative dosage range of 180-3650 mcg. Five of them (15.63%) were smokers.

Seventeen patients (eight females and nine males) had normal BMD (mean age 34.94 ± 11.41 years, 47.1% female) and fifteen (five females and 10 males) had low BMD (mean age 40.03 ± 15.87 years, 33.3% female). In the low BMD group, three patients had osteoporosis and 12 had osteopenia.

Bronchiectasis confirmed by high resolution computed tomography was observed in 20 patients. There was no significant difference in BMD between those with and without bronchiectasis (p=0.784). Half of the patients had splenomegaly (50%). Five patients had suffered from pathological bone fractures.

Serum calcium levels were significantly lower and ALP levels were significantly higher in the low BMD group (respectively p=0.021 and p=0.018). There was no statistically significant difference between the groups in terms of gender, age, lymphocyte count, platelet count, neutrophil count, and the presence of lymphopenia, bronchiectasis or splenomegaly. Baseline demographic, clinical and laboratory parameters of the patients with osteopenia and osteoporosis are listed in Table I.

When the relationship between the patients' biochemical parameters and BMD was evaluated, ALP levels showed a negative correlation with both femur and lumbar T and Z scores (p=0.015, p=0.011, p=0.017, p=0.009, respectively) and the lymphocyte count was found to be positively correlated with both femur and lumbar T and Z scores (p=0.029, p=0.006, p=0.019, p=0.024, respectively) (Table II).

Univariate regression analysis revealed that lymphopenia (odds ratio, OR:6.562, 95% confidence interval, CI: 1.095-39.324, p=0.039) was significantly associated with low BMD (Table II). Multivariate regression analysis showed that higher alkaline phosphatase levels (OR:1.017, 95% CI:1.001-1.033, p=0.041), lower folic acid levels (OR:1.284, 95% CI:1.007-1.637, p=0.043), and lymphopenia (OR:0.091, 95% CI:0.011-0.754, p=0.026) were also independent predictors for low BMD (Table III).

DISCUSSION

Low BMD is a worldwide public health problem. In the present study, we investigated low BMD and associated factors in adult patients with CVID. Fifteen patients with CVID (five females and 10 males) had low BMD (three patients with osteoporosis and 12 patients with osteopenia). Low BMD has been found to be linked with a lower level of folic acid and lymphopenia, in addition to elevated ALP in these patients. As far as we are aware, this is the first study specifying this suggestion in adult CVID patients.

Delayed diagnosis, usually six to eight years in patients with CVID, is a common problem that may cause additional complications (7). Sustained inflammation due to infectious or non-infectious complications and/or inappropriate treatment may influence the bone density. However, there was no statistically significant difference between patients with low BMD and normal BMD in terms of diagnostic delay in our study group.

Lymphopenia is considered as an independent predictor of mortality, especially in cases of hospitalization due to pneumonia (14). Lymphopenia also increases the risk of

Table I: Baseline demographic, clinical, and laboratory parameters of the study population.

	Total (n=32)	Low BMD (n=15)	Normal BMD (n=17)	P
Gender (female), n, %	13 (40.6)	5 (33.3)	8 (47.1)	0.43
Age	37.33 ± 13.70	40.03 ± 15.87	34.94 ± 11.41	0.301
Lymphocyte count (800-5500/mm^3)	1745.5 ± 1346.80	1124.73 ± 614.01	2293 ± 1582.55	0.120
Lymphopenia, n, % (Lymphocyte count < 800/mm^3)	9 (28.1)	7 (46.7)	2 (11.8)	**0.035**
B lymphocyte (%)	6.81 ± 5.16	7.2 ± 4.38	6.46 ± 5.89	0.697
BMI (kg/m^2)	24.47 ± 4.74	24.08 ± 5.34	24.82 ± 4.28	0.669
Bronchiectasis, n, %	20 (62.5)	9 (64.7)	11 (60)	0.784
FEV1, %	73.77 ± 17.77	69.67 ± 5.31	77.39 ± 3.53	0.226
Smoking n, %	5 (15.6)	2 (17.6))	3 (13.3)	0.737
Cumulative dosage of inhaled corticosteroid treatment (mg, total)	0 (0-3650)	730 (0-3650)	0 (0-2920)	0.114
Splenomegaly, n, %	16 (50)	10 (66.7)	6 (35.3)	0.077
Pathologic fracture, n, %	5 (15.6)	3 (20)	2 (11.8)	0.522
Diagnostic delay, (months)	102.03 ± 98.19	111.60 ± 78.03	93.58 ± 114.86	0.613
Vitamin B12 (192-961 pg/ml)	383.34 ± 134.88	428.20 ± 145.17	343.76 ± 115.15	0.770
Folic acid (3.1-19.9 ng/ml)	8.01 ± 4.22	6.93 ± 3.21	9.24 ± 4.98	0.126
Calcium (8.5-10.2 mg/dl)	9.11 ± 0.97	8.88 ± 0.11	9.32 ± 0.14	**0.021**
Phosphorus (2.3-4.7 mg/dl)	3.48 ± 0.55	3.59 ± 0.49	3.38 ± 0.60	0.286
Parathyroid hormone (1-67 pg/ml)	45.90 (15.70-670.0)	46.8 (15.7-670)	45 (18.5-197)	0.911
Vitamin D (> 30 ng/ml)	12.39 ± 7.15	13.22 ± 7.78	11.66 ± 6.71	0.548
Alkaline phosphatase (40-150 u/L)	98 (8.30-490)	127 (48-490)	79 (8.3-241)	**0.018**
Ig G (7-16 g/L)	9.21 (3.25-13.10)	8.75 (3.25-12.0)	9.5 (3.88-13.10)	0.132
Ig M (0.4-2.3 g/L)	0.19 (0.04-10.60)	0.19 (0.04-4.73)	0.23 (0.05-10.60)	0.455
Ig A (0.7-4 g/L)	6.5 (0-16)	7 (0-14)	6(0-16)	0.132

BMI: Body Mass Index, **FEV1:** Forced expiratory volume in one second, **Ig:** Immunoglobulin.

Table II: Logistic regression analysis of possible risk factors associated with low BMD.

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	p	OR (95% CI)	p
Alkaline phosphatase	1.015 (1.000-1.030)	0.057	1.017 (1.001-1.033)	**0.041**
Lymphopenia	6.562 (1.095-39.324)	**0.039**	0.091 (0.011-0.754)	**0.026**
Lower folic acid level	1.157 (0.954-1.404)	0.139	1.284 (1.007-1.637)	**0.043**
Splenomegaly	0.273 (0.063-1.178)	0.082	0.604 (0.590-6.206)	0.672
Vitamin B12	1.005 (0.999-1.011)	0.083	1.007 (0.997-1.016)	0.171
Calcium	0.162 (0.030-0.877)	0.55	0.217 (0.019-2.462)	0.217

bacterial superinfections (15). Although, CVID is accepted as a humoral immunodeficiency, many cellular immunity-related distortions such as decreased T lymphocyte proliferation in response to mitogens and antigens, reduced number of T regulatory cells, and reduced thymic output have been identified (16-18). These disorders have been shown to be associated with chronic inflammation in CVID patients (17), and this has been shown to adversely

Table III: Baseline demographic, clinical, and laboratory parameters of the patients with osteopenia and osteoporosis.

	Low BMD (n=15)	Osteopenia (n=12)	Osteoporosis (n=3)	p
Gender (female), n, %	5 (33.3)	5 (41.7)	0	0.505
Age	40.03 ± 15.87	36.95 ± 15.90	52.33 ± 9.45	0.080
Lymphocyte count (800-5500/mm^3)	1124.73 ± 614.01	1174.08 ± 625.77	927.33 ± 642.09	0.591
Lymphopenia, n, % (Lymphocyte count < 800/mm^3)	7 (46.7)	6 (50)	1 (33.3)	0.999
B lymphocyte (%)	7.2 ± 4.38	7.92 ± 4.54	4.33 ± 2.31	0.099
BMI (kg/m^2)	24.08 ± 5.34	24.96 ± 4.69	20.57 ± 7.47	0.418
Bronchiectasis, n, (%)	9 (64.7)	6 (50)	3 (100)	0.229
FEV1, %	69.67 ± 5.31	73.92 ± 17.13	52.67 ± 28.38	0.323
Smoking, n, (%)	2 (13.3)	2 (16.7)	0	0.999
Cumulative dosage of inhaled corticosteroid treatment (mg, total)	730 (0-3650)	540 (0-3650)	730 (0-730)	0.840
Splenomegaly, n, (%)	10 (66.7)	8 (66.7)	2 (66.7)	0.999
Pathologic fracture, n, (%)	3 (20)	2 (16.7)	1 (33.3)	0.516
Diagnostic delay, (months)	111.60 ± 78.03	107.50 ± 64.54	128.00 ± 138.56	0.829
Vitamin B12 (192-961 pg/ml)	428.20 ± 145.17	421.58 ± 149.70	454.67 ± 151.40	0.756
Folic acid (3.1-19.9 ng/ml)	6.93 ± 3.21	9.81 ± 5.10	6.95 ± 4.52	0.402
Calcium (8.5-10.2 mg/dl)	8.88 ± 0.11	8.97 ± 0.43	8.52 ± 0.30	0.093
Phosphorus (2.3-4.7 mg/dl)	3.59 ± 0.49	3.55 ± 0.51	3.79 ± 0.40	0.420
Parathyroid hormone (1-67 pg/ml)	46.8 (15.7-670)	46.65 (15.7-288)	124 (17.2-670)	0.536
Vitamin D (> 30 ng/ml)	13.22 ± 7.78	14.26 ± 8.12	9.07 ± 5.35	0.242
Alkaline phosphatase (40-150 u/L)	127 (48-490)	79 (8.3-241)	79 (8.3-241)	**0.031**
IgG (7-16 g/L)	8.75 (3.25-12.0)	8.83 (3.25-11.0)	7.8 (6.75-12.0)	0.945
IgM (0.4-2.3 g/L)	0.19 (0.04-4.73)	0.19 (0.04-4.73)	0.22 (0.19-1.35)	0.295
IgA (0.7-4 g/L)	7 (0-14)	0.25 (0.01-1.04)	0.26 (0.24-0.26)	0.633

affect BMD (19). In the current study, the lymphocyte count was found to be positively correlated with both femur and lumbar T and Z scores, and this finding is compatible with the literature. On the other hand, CVID patients with lymphopenia and T cell abnormalities may have severe opportunistic infections and a higher incidence of splenomegaly, lymphoma and granuloma than other patients with CVID (20). This immune dysregulation requires the use of immunosuppressive therapeutic agents that adversely affect BMD. Lymphopenia may also be part of late onset combined immunodeficiency and the side effects of immunosuppressive drugs.

ALP is a specific and sensitive marker of bone formation and can be used to predict bone loss and risk of fracture, especially in post-menopausal women (21). Elevated levels of ALP are usually reduced to a normal range by bisphosphonate treatment (22). Ivaska et al. have shown that increased serum levels of bone turnover markers such as ALP are associated with increased bone loss (23). Another study has shown that increased ALP levels are associated with increased vertebral and non-vertebral fractures, independent of BMD (24,25). In the current study, ALP levels had a negative correlation with both lumbar and femur BMD scores in line with the mentioned studies. In addition, ALP levels were significantly different between CVID patients with osteopenia and with osteoporosis. The elevated ALP was found to be an independent predictor for low BMD in patients with CVID. Mohebbi et al. reported that ALP levels had no correlation with low BMD. The study group in that report was more heterogenous and included both adult and child patients with either CVID or X-linked agammaglobulinemia (XLA). This may explain these unexpected results.

Bone mineral loss is a well-defined complication in chronic lung diseases (26). Bronchiectasis and chronic lung disease may develop due to the frequent respiratory infections in patients with CVID, and lung function loss may occur due to granulomatous lung disease and interstitial lung involvement (27). In addition, patients who develop chronic lung disease use a higher dose of immunosuppressants to control their respiratory complaints and are immobilized, which may lead to bone mineral loss (26, 28). In the current study, the FEV1 values correlated with BMD scores in the femur.

It is well known that calcium and vitamin D levels are some of the most important modifiable factors for bone health management (29). Even though calcium levels were lower in the low BMD group, the univariate regression analysis showed that calcium was not an independent predictor for osteoporosis in patients with CVID. Vitamin D levels were low in all CVID patients included in this study. Furthermore, there was no meaningful difference between patients with low and normal BMD in terms of vitamin D. In a 2017 report, biochemical markers including calcium, phosphorus and parathyroid hormone (PTH) levels were not correlated with the BMD (30). Our study results were in concordance with this report. In our study, the serum calcium levels were weakly correlated only with T scores. However, there was no correlation between BMD and the vitamin D, PTH, and phosphorus levels. However, another study conducted in pediatric patients with CVID has shown that low dietary calcium intake and low 25(OH) vitamin D levels are associated with low BMD (31). We used serum calcium levels rather than daily calcium intake and our population consisted only of adult CVID patients, which might be the main reasons for the difference between the two studies. Vitamin D levels were low in all CVID patients included in our study, and this may be another reason for the different results between the studies.

In addition to these obvious factors, reduced vitamin B12 and folic acid levels also affect bone metabolism negatively (32). Folic acid supplementation reduces the homocysteine level, which is a risk factor for osteoporosis (33). Salari et al. reported that 1 mg of folic acid supplementation for 6 months had an impact on the rate of bone metabolism (34). In another study, folic acid deficiency, but not vitamin B12 deficiency, was found to be an important factor in vertebral BMD decline (35). In parallel with these findings, we also found that lower folic acid levels were an independent predictor for low BMD. Baris et al. have demonstrated that a low folic acid level is a risk factor for reduced BMD in pediatric patients with CVID (31). Our results were concordant with this data and redraw attention to the importance of lower folic acid levels for patients with low BMD. There was a negative but insignificant correlation between vitamin B12 and folic acid levels and the BMD in the current study. The association of low folic acid levels and osteoporosis was established in another study in a mixed pediatric-adult population by Mohebbi et al. That study used T scores in patients aged higher than 18 years, and Z score in patients aged lower than 18 years (30). In contrast to this variant method, we used Z scores for males aged lower than 55 years and premenopausal women (13), and included only adult patients in our study (13). In conclusion, even if our study has some limitations such as a small number for the study population, a single center experience, and a cross-sectional design, we recommend that clinical immunologists should to be alert for bone loss in CVID patients, especially those with low folic acid and high ALP levels, and lymphopenia.

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REFERENCES

1. Gathmann B, Mahlaoui N, Gerard L, Oksenhendler E, Warnatz K, Schulze I, et al. Clinical picture and treatment of 2212 patients with common variable immunodeficiency. J Allergy Clin Immunol 2014;134(1):116-26.
2. Verma N, Grimbacher B, Hurst JR. Lung disease in primary antibody deficiency. Lancet Respir Med 2015;3(8):651-60.
3. Azizi G, Abolhassani H, Kiaee F, Tavakolinia N, Rafiemanesh H, Yazdani R, et al. Autoimmunity and its association with regulatory T cells and B cell subsets in patients with common variable immunodeficiency. Allergol Immunopathol (Madr) 2018;46(2):127-35.
4. Tak Manesh A, Azizi G, Heydari A, Kiaee F, Shaghaghi M, Hossein-Khannazer N, et al. Epidemiology and pathophysiology of malignancy in common variable immunodeficiency? Allergol Immunopathol (Madr) 2017;45(6):602-15.
5. Uzzan M, Ko HM, Mehandru S, Cunningham-Rundles C. Gastrointestinal disorders associated with common variable immune deficiency (CVID) and chronic granulomatous disease (CGD). Curr Gastroenterol Rep 2016;18(4):17.
6. Maglione PJ. Autoimmune and lymphoproliferative complications of common variable immunodeficiency. Curr Allergy Asthma Rep 2016;16(3):19.

7. Ballow M. Managing comorbid complications in patients with common variable immunodeficiency. Ann Allergy Asthma Immunol 2013;111(Suppl 6):S6-9.
8. Briot K, Geusens P, Em Bultink I, Lems WF, Roux C. Inflammatory diseases and bone fragility. Osteoporos Int 2017;28(12):3301-14.
9. Tanaka Y, Nakayamada S, Okada Y. Osteoblasts and osteoclasts in bone remodeling and inflammation. Curr Drug Targets Inflamm Allergy 2005;4(3):325-8.
10. D'Amelio P, Sassi F. Gut Microbiota, Immune System, and Bone. Calcif Tissue Int 2018;102(4):415-25.
11. Conley ME, Notarangelo LD, Etzioni A. Diagnostic criteria for primary immunodeficiencies. Representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999;93(3):190-7.
12. Melton LJ 3rd, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. How many women have osteoporosis? J Bone Miner Res 1992;7(9):1005-10.
13. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ 3rd, Khaltaev N. A reference standard for the description of osteoporosis. Bone 2008;42(3):467-75.
14. Bellelli V, d'Ettorre G, Celani L, Borrazzo C, Ceccarelli G, Venditti M. Clinical significance of lymphocytopenia in patients hospitalized with pneumonia caused by influenza virus. Crit Care 2019;23(1):330.
15. Zhou F, Li H, Gu L, Liu M, Xue CX, Cao B, et al. Risk factors for nosocomial infection among hospitalised severe influenza A(H1N1)pdm09 patients. Respir Med 2018;134:86-91.
16. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 1999;92(1):34-48.
17. Fevang B, Yndestad A, Sandberg WJ, Holm AM, Muller F, Aukrust P, et al. Low numbers of regulatory T cells in common variable immunodeficiency: Association with chronic inflammation in vivo. Clin Exp Immunol 2007;147(3):521-5.
18. Serana F, Airo P, Chiarini M, Zanotti C, Scarsi M, Frassi M, et al. Thymic and bone marrow output in patients with common variable immunodeficiency. J Clin Immunol 2011;31(4):540-9.
19. Adami G, Fassio A, Rossini M, Caimmi C, Giollo A, Orsolini G, et al. Osteoporosis in Rheumatic Diseases. Int J Mol Sci. 2019;20(23).
20. Malphettes M, Gerard L, Carmagnat M, Mouillot G, Vince N, Boutboul D, et al. Late-onset combined immune deficiency: A subset of common variable immunodeficiency with severe T cell defect. Clin Infect Dis 2009;49(9):1329-38.
21. Eastell R, Hannon RA. Biomarkers of bone health and osteoporosis risk. Proc Nutr Soc 2008;67(2):157-62.
22. Mukaiyama K, Kamimura M, Uchiyama S, Ikegami S, Nakamura Y, Kato H. Elevation of serum alkaline phosphatase (ALP) level in postmenopausal women is caused by high bone turnover. Aging Clin Exp Res 2015;27(4):413-8.
23. Ivaska KK, Lenora J, Gerdhem P, Akesson K, Vaananen HK, Obrant KJ. Serial assessment of serum bone metabolism markers identifies women with the highest rate of bone loss and osteoporosis risk. J Clin Endocrinol Metab 2008;93(7):2622-32.
24. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: The OFELY study. J Bone Miner Res 2000;15(8):1526-36.
25. Delmas PD, Licata AA, Reginster JY, Crans GG, Chen P, Misurski DA, et al. Fracture risk reduction during treatment with teriparatide is independent of pretreatment bone turnover. Bone 2006;39(2):237-43.
26. Sarkar M, Bhardwaj R, Madabhavi I, Khatana J. Osteoporosis in chronic obstructive pulmonary disease. Clin Med Insights Circ Respir Pulm Med 2015;9:5-21.
27. Aytekin G, Cölkesen F, Yıldız E, Arslan S. Risk factors of bronchiectasis in adult patients with common variable immunodeficiency. Asthma Allergy Immunol 2019;17:160-5.
28. Gregg EW, Cauley JA, Seeley DG, Ensrud KE, Bauer DC. Physical activity and osteoporotic fracture risk in older women. Study of Osteoporotic Fractures Research Group. Ann Intern Med 1998;129(2):81-8.
29. Fratoni V, Brandi ML. B vitamins, homocysteine and bone health. Nutrients 2015;7(4):2176-92.
30. Mohebbi A, Azizi G, Tavakolinia N, Abbasi F, Sayarifard F, Karimipour M, et al. Comparison of bone mineral density in common variable immunodeficiency and X-linked agammaglobulinaemia patients. Endocr Metab Immune Disord Drug Targets 2017;17(2):134-40.
31. Baris S, Ozen A, Ercan H, Karakoc-Aydiner E, Cagan H, Ozdemir C, et al. Osteoporosis: An ignored complication of CVID. Pediatr Allergy Immunol 2011;22(7):676-83.
32. Swart KM, van Schoor NM, Lips P. Vitamin B12, folic acid, and bone. Curr Osteoporos Rep 2013;11(3):213-8.
33. Almassinokiani F, Kashanian M, Akbari P, Mossayebi E, Sadeghian E. Folic acid supplementation reduces plasma homocysteine in postmenopausal women. J Obstet Gynaecol 2016;36(4):492-5.
34. Salari P, Abdollahi M, Heshmat R, Meybodi HA, Razi F. Effect of folic acid on bone metabolism: A randomized double blind clinical trial in postmenopausal osteoporotic women. Daru 2014;22:62.
35. Cagnacci A, Bagni B, Zini A, Cannoletta M, Generali M, Volpe A. Relation of folates, vitamin B12 and homocysteine to vertebral bone mineral density change in postmenopausal women. A five-year longitudinal evaluation. Bone 2008;42(2):314-20.