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Original Article

The relationship between vitamin D level and disease activity and focal erosion in rheumatoid arthritis

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Abstract

Aim: Bone loss,fragility,and fractures are well-described complications that affect quality of life, morbidity, and health care costs during the course of rheumatoid arthritis (RA). Besides its well-known role in bone metabolism, vitamin D is also an important immune modulator, meant to affect the disease activity of rheumatic disorders. However, conflicting results have been demonstrated about the relationship between levels of vitamin D and disease activity in RA. Primary aim of was to compare vitamin D levels and Bone Mineral Density (BMD) values between RA and control groups.The secondary aim was to assess the correlations between vitamin D and disease activity and radiologic damage in RA.

Material and Methods: A total of 41 RA patients and 40 healthy controls were included in this study. The patient and control groups were between the ages of 18 and 65. Disease activity score 28 (DAS-28) was used to determine the severity of disease.Sharp/van der Heijde method was performed to evaluate the radiologic changes.Dual energy X-ray absorptiometry (DEXA) was performed to measure Bone Mineral Density (BMD).Enzyme-Linked Immunosorbent Assay (ELISA) method was used to measure serum D vitamin concentrations.

Results: Vitamin D levels, the BMD-lumbar spine, BMD-femur total and BMD-femur neck values were significantly lower in the patient group ($p = 0.012$, $p < 0.001$, $p < 0.001$ and $p < 0.001$). No significant correlations were detected between vitamin D levels and BMD values, disease activity, and radiologic damage scores ($p > 0.05$). DAS-28 was significantly and negatively correlated with BMD values ($p < 0.05$).

Conclusion: Our study suggests that RA patients have lower vitamin D levels, BMD-lumbar spine, BMD-femur total and BMD-femur neck values. Higher disease activity increases bone loss in RA. Vitamin D levels and BMD values should be monitored for the risk of osteoporosis and fracture in RA.

Keywords: Rheumatoid Arthritis; Vitamin D; Bone Mineral Density; Disease Activity; Radiologic Damage.

INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune rheumatic disorder with inflammation, synovitis, peripheral symmetrical arthritis, synovial cell proliferation and extra-articular manifestations (1,2). The etiopathogenesis of RA is complex and environmental factors induce disease in genetically sensitive individuals (3). Osteopenia and osteoporosis (OP) are well known complications of rheumatic diseases, particularly RA.Three types of osteoporosis have been described in RA: focal bone erosion, periarticular OP, and generalized OP (4). Increased disease activity, immobilization due to the pain and treatment with glucocorticoids are the major risk factors increasing bone loss in RA (5). Proinflammatory cytokines induce erosions and periarticular OP by stimulating osteoclast formation and activation. Additionally, osteoclasts are more likely to have increased functional activity in generalized OP. Thus, appropriate control of disease activity may reduce bone loss and low energy fractures in RA (6).

Vitamin D, defined as a prohormone, influences the immune system as well as bone metabolism. Vitamin D receptors that mediate immune system regulatory functions have been isolated from active dendritic cells, antigen presenting cells, T and B lymphocytes (7,8). Vitamin D decreases the production of proinflammatory mediators such as interleukin 1 (IL-1), IL-6, IL-17 and

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tumor necrosis factor alpha (TNF-α) by inhibiting the immunological response of Th1 cells (9). Therefore, the risk of infection and autoimmune disease is increasing in case of the insufficient or deficient levels of vitamin D (10). Although some studies have demonstrated the relationship between levels of vitamin D and disease activity in RA, this issue has not been fully clarified in the literature (11).

Our primary aim was to compare vitamin D levels and bone mineral density (BMD) values between RA and control groups. The secondary aim was to assess the correlations between vitamin D and disease activity and radiologic damage in RA.

MATERIAL and METHODS

Study Design & Participants

This study has a case control design. A total of 52 RA patients who applied to a physical medicine and rehabilitation polyclinic and 40 healthy controls were assessed. Patients fulfilled the RA classification criteria of the 2010 American College of Rheumatology/ European League against Rheumatism (12). The patient and control groups were between the ages of 18 and 65.

Exclusion criteria include a history of metabolic bone diseases, recent fractures, malnutrition, neoplasia, chronic infection, inflammatory bowel disease, diabetes mellitus, thyroid/parathyroid dysfunction, liver/renal diseases, drug use affecting metabolism of bone such as bisphosphonates, vitamin D supplementations, pregnancy, and breast-feeding.

After the application of the exclusion criteria, 41 RA patients were remained and two groups were formed according to medication use, patients receiving TNF-α inhibitor and those receiving Disease-Modifying Antirheumatic Drug (DMARD) groups.Patients in the TNF-α inhibitor group were using infliximab, golimumab, adalimumab, or etanercept. Patients in the DMARD group were using methotrexate, salazopyrine or hydroxychloroquine.

Data Sources & Measurement

Data were recorded including age, sex, body mass index (BMI), duration of disease.Disease activity score 28 (DAS-28) was used to determine the severity of disease. We used c reactive protein (CRP) concentrations for calculating DAS-28.

Radiologic Assessment

Sharp/van der Heijde method was performed to evaluate the radiologic changes.Radiographs were scored by a radiologist who was blinded to the patients' identity. Joint space narrowing and erosion were determined and scored using the radiographs of hands and feet (13).

Dual energy X-ray absorptiometry (DEXA) (HOLOGIC 4500 A) was performed to measure BMD in the lumbar spine (L1 - L4 anterior - posterior), total femur, and femur neck. The results are expressed as g/cm^2.

Radiologic assessments were performed at the same day of the physical examination.

After the physical examination, blood samples were obtained from participants between 8.00–10.00 AM. Standard laboratory techniques were used to measure CRP (Cobas Integra 400 plus, Rotkreuz, Switzerland) and the erythrocyte sedimentation rate (ESR) (EventusVacuPlus ESR 100, Ankara, Turkey) concentrations.Enzyme-Linked Immunosorbent Assay (ELISA) method was used to measure serum 25-hydroxyvitamin D (25-OHD) levels and results expressed in ng / mL (normal value ≥ 30 ng / ml).

Ethical Consideration

This study has been approved by the Medical Ethics Committee of Kahramanmaras Sutcu Imam University.

Statistical Analysis

Statistical Package for Social Sciences for Windows version 20.0 package program (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis.Mean ± standard deviation, median (minimum-maximum), and number were used for the expression of results. Distribution of data was evaluated using the Shapiro-Wilk test. Determination the differences in the categorical variables was performed using the Chi-Square test. Comparison of independent groups was performed using the independent sample t test or Mann-Whitney U test according to the distribution of data. Spearman's rho test was performed for the correlation analysis. The statistical significance level was accepted as $p < 0.05$.

RESULTS

In our study, 41 RA patients (31 females, 10 males) and 40 healthy controls (24 females, 16 males) were included. The mean ages in the patient and control groups were 48.80 ± 11.63 and 44.65 ± 11.40 years.Age, sex and BMI were not significantly different between the patient and control groups ($p > 0.05$) (Table 1).

Table 1. Demographic data of patient and control groups

	Patient Group (n = 41)	Control Group (n = 40)	P
Age (years)	48.80 ± 11.63	44.65 ± 11.40	0.109
Sex			
Female (n)	31	24	0.132
Male (n)	10	16	
BMI (kg/m^2)	28.33 ± 5.65	26.97 ± 4.27	0.225

n: number; BMI: body mass index

Vitamin D level, the BMD-lumbar spine, BMD-femur total and BMD-femur neck values were significantly lower in the patient group ($p = 0.012$, $p < 0.001$, $p < 0.001$ and $p < 0.001$) (Table 2).

No significant differences were detected between the TNF-α inhibitor (n = 17) and DMARD (n = 24) groups in terms of 25-OHD, ESR and CRP concentrations, BMD-lumbar spine, total BMD-femur and BMD - femur neck values ($p > 0.05$).

No significant correlations were detected between 25-OHD concentrations and symptom duration,Sharp/van

der Heijde scores, DAS-28, ESR, CRP,BMD-lumbar spine, BMD-femur total and BMD-femur neck in the patient group (p > 0.05) (Table 3).

No significant correlations were detected between ESR, CRP and BMD values (p > 0.05). DAS-28 was significantly and negatively correlated with BMD-lumbar spine, BMD-femur total and BMD-femur neck values (r = -0.504, p = 0.001; r = -0.447, p = 0.003 and r = -0.411, p = 0.008, respectively).

Table 2. Comparison of bone mineral density and laboratory parameters between patient and control groups

	Patient Group (n = 41)		Control Group (n = 40)		P
	median	min-max	Median	min-max	
Vitamin D (ng/ml)	16.66	1.02-58	21.44	6.70-65	0.012
BMD – lumbar spine (g/ cm^2)	0.89	0.67-1.15	0.96	0.68-1.32	< 0.001
BMD – femur total (g/ cm^2)	0.83	0.59-1.07	0.98	0.81-1.42	< 0.001
BMD – femur neck (g / cm^2)	0.73	0.51-1.00	0.92	0.74-1.34	< 0.001
ESR (mm / h)	20	2-70	5.50	1-32	< 0.001
CRP (mg / L)	4.10	0.10-59	1.51	0.05-13.20	0.002

n: number; min: minimum; max: maximum; BMD: bone mineral density; ESR: erythrocyte sedimentation rate; CRP: C - reactive protein

Table 3. Correlation analysis of clinic and laboratory parameters with 25-hydroxyvitamin D

	rho	p
Symptom duration	0.249	0.117
Sharp/van der Heijde- narrowing hand score	-0.001	0.994
Sharp/van der Heijde- narrowing foot score	0.143	0.372
Sharp/van der Heijde- total narrowing score	0.062	0.702
Sharp/van der Heijde- erosion hand score	0.109	0.486
Sharp/van der Heijde- erosion foot score	0.045	0.780
Sharp/van der Heijde- total erosion score	0.142	0.376
Sharp/van der Heijde-total score	0.108	0.503
DAS-28	-0.205	0.199
ESR (mm/h)	-0.196	0.218
CRP (mg/L)	-0.228	0.151
BMD - lumbar spine (g/cm^2)	-0.019	0.908
BMD - femur total (g/cm^2)	-0.047	0.771
BMD - femur neck (g/cm^2)	-0.067	0.677

DAS-28: disease activity score 28; ESR:erythrocyte sedimentation rate; CRP: C - reactive protein; BMD: bone mineral density

DISCUSSION

This study suggests that levels of 25-OHD were significantly lower in RA patients. No significant correlations were detected between 25-OHD concentrations and disease activity, radiologic changes and BMD values in RA patients.Vitamin D is a secosteroid hormone and has substantial skeletal and non-skeletal biologic functions. Vitamin D deficiency causes a decrease in intestinal absorption of calcium and phosphorus. In the early period of vitamin D deficiency, hypophosphatemia is more prominent than hypocalcemia. If vitamin D deficiency persists, hypocalcemia develops and triggers secondary hyperparathyroidism that will cause phosphaturia. Vitamin deficiency induces the levels of alkaline phosphatase and causes variations in levels bone turnover markers (14).

Immune cells including macrophages, T and B lymphocytes, and dendritic cells have been shown to express vitamin D receptors (15). Vitamin D influences immune responses via innate and adaptive immune systems. Vitamin D suppresses immune globulin production, B cell differentiation and T cell proliferation. Levels of proinflammatory cytokines are decreased and the immune activity of macrophages is inhibited. Additionally, vitamin D increases the anti-inflammatory response by activating T helper-2 and regulator T cell responses (16,17). Conflicting results have been demonstrated about the vitamin D and RA link. Similar to our results; Baykal et al. (18), Rossini et al. (19), Kostoglou-Athanassiou et al. (20) and Kroger et al. (21) reported lower concentrations of vitamin D in RA patients. In contrast; Nielen et al. (22), Cutolo et al. (23) and Turhanoglu et al. (24) reported no difference in vitamin D concentrations between RA patients and controls. In agreement with our results, no inverse correlations were found between vitamin D concentrations and disease activity in RA patients (25,26,27). On the contrary, significant inverse correlations have been reported between vitamin D concentrations and disease activity (23,28,29).

There may be several explanations for the differences in the above mentioned studies. Variations in sample size, study population, ethnicity and season may cause these discrepancies. Additionally, severity of disease, vitamin D supplementation use, dietary vitamin D intake, disease duration, physical activity level and medication use may also affect the results.

In our study, BMD-lumbar spine, BMD-femur total and BMD-femur neck values were significantly lower in RA patients. Bone loss and increased fracture risk have been demonstrated in RA patients (30). Kröger et al. (31) and Ladder et al. (32) reported lower BMD values in RA patients. Causes of bone loss in RA include joint inflammation, disease activity, reduced mobility, and steroid use (33). DAS-28, disease activity parameter, was significantly and inversely correlated with BMD values in this study. Shibuya et al. (34) reported that disease activity, duration of disease and BMI were associated with BMD in RA patients. Bone loss was predominantly observed in peripheral joints in this study. Early development of osteoporosis at the peripheral joints suggests that inflammation, cytokines and synovitis mainly affect bone loss in RA patients. In another study, negative correlations have been demonstrated between disease activity and BMD values (35). On the contrary, Sivas et al. (36) reported

no significant correlations between disease activity and lumbar and femur neck BMD values. Cytokines have direct and indirect effects on peripheral joints and systemic bones and enhances osteoclastogenesis in the tissue. Additionally, cytokines play a key regulatory role on RANKL and osteoprotegerin which are the important mediators for osteoclast differentiation and activation.Cytokines activate osteoclastogenesis via RANKL which controls the activation, differentiation and survival of osteoclasts (37). Studies on normal populations have shown that low levels of inflammatory markers prevent bone loss and resorption (38). Another explanation for the inflammation and osteoporosis link might be that higher disease activity decreases physical activity and muscle strength. This condition causes a decrease in the loading on the bones and leads to bone loss in RA. In our study, BMD values were not found to be significantly different between the TNF-α inhibitor and DMARD groups. These results may be due to the lack of differences in vitamin D, ESR, and CRP levels between the groups.

This study has some limitations. The sample size is small. The physical activity level, dietary habits and sunlight exposure frequencies were not assessed. This study has a cross-sectional design and patients were not followed-up prospectively. We did not question previous steroid use. RF or anti CCP levels were not evaluated in all RA patients. Finally; calcium, phosphorus, alkaline phosphatase, parathormone and other bone turnover markers were not measured.

CONCLUSION

In conclusion, we found lower vitamin D concentrations in RA patients. Vitamin D concentrations were not associated with radiologic damage, disease activity parameters and BMD values. BMD values were lower than the healthy controls and disease activity was negatively correlated with BMD values. Disease activity and inflammation increase bone loss and the reduction of BMD starts in the early phase of RA; continues throughout the disease. Therefore, patients whose disease activity is severe and whose inflammation cannot be suppressed despite treatment should be monitored for the risk of osteoporosis and fracture. Vitamin D is a potential factor in the etiopathogenesis of RA. We believe that vitamin D levels should also be monitored and should be replaced if they are found to be deficient in RA patients.

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