

CLINICAL SCIENCE

Vitamin D status in patients with Behcet's Disease

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OBJECTIVES: This study investigated the serum 25-hydroxyvitamin D levels of patients with Behcet's Disease.

DESIGN AND METHODS: Thirty-two patients with Behcet's Disease and 31 matched healthy controls were enrolled in this study. The erythrocyte sedimentation rate (ESR) and the levels of C-reactive protein (CRP), serum 25-hydroxyvitamin D, calcium (Ca), phosphate (P), and total alkaline phosphatase (ALP) were measured in both groups.

RESULTS: There were no significant differences between the two groups regarding demographic data. The serum 25-hydroxyvitamin D levels of patients and controls were 13.76 (range: 4.00-35.79) and 18.97 (range: 12.05-36.94) ng/ml, respectively. In patients with Behcet's Disease, 25-hydroxyvitamin D values were significantly lower than those of the healthy controls ($p < 0.001$). Serum Ca, P, and ALP levels were similar in both groups. Serum ESR and CRP levels were significantly higher in patients than controls ($p < 0.05$). There was no correlation between 25-hydroxyvitamin D levels and age, body mass index (BMI), disease duration, ESR, or CRP levels. Multivariate regression analysis parameters showed that smoking, alcohol intake, and use of colchicine were the main predictors of 25-hydroxyvitamin D levels. Of the parameters studied, the largest impact was due to colchicine therapy ($p < 0.001$). We did not find a significant relationship between the use of corticosteroids and 25-hydroxyvitamin D levels.

CONCLUSION: Our results suggest that serum 25-hydroxyvitamin D levels are decreased in patients with Behcet's Disease. Smoking, alcohol intake, and use of colchicine appear to affect vitamin D levels.

KEYWORDS: Behcet's Disease; vitamin D, inflammation; 25-hydroxyvitamin D; colchicine.

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INTRODUCTION

Behcet's Disease is a chronic inflammatory disease with exacerbations and remissions characterized by recurrent orogenital ulcerations, ocular manifestations, arthritis, and vasculitis. In addition, neurological and large vessel involvement can occur in some cases.¹ Occasionally it appears associated with ankylosing spondylitis.² The infiltration of lymphocytes and monocytes through small veins without microscopic changes in the vessel walls are major features in the inflamed tissues.³ The etiology and pathogenesis of Behcet's Disease have not been clearly defined. However, several genetic, environmental, and immunological factors have been suggested as causative factors in this disease.⁴ In addition, the role of the *HLA-B51* gene in genetic susceptibility to Behcet's Disease has been defined in recent years.⁵⁻⁶

Vitamin D has long been known to be important for bone health and turnover.⁷ In recent studies, vitamin D has been demonstrated to play a significant role in malignancy,

immune system functioning, and cardiovascular events.⁸⁻¹⁰ The measurement of serum 25-hydroxyvitamin D levels, commonly used by clinicians, is accepted as a clinical indicator of vitamin D status because of its correlation with low vitamin D values.¹¹ The metabolite 1,25-dihydroxyvitamin D is formed by 1-hydroxylation of 25-hydroxyvitamin D in the kidneys.⁸ Although it is the active metabolite of vitamin D, 1,25-dihydroxyvitamin D serum values do not correlate well with vitamin D deficiency. Therefore, these values are not preferred for routine testing of vitamin D levels.

Vitamin D deficiency is particularly common in patients with rheumatological disorders, such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).¹² Vitamin D status has been inversely correlated with disease activity in those disorders due to the immunomodulatory effects of vitamin D.^{13,14} Vitamin D has been proposed as a new preventive treatment of inflammatory diseases. Environmental and inflammatory factors, renal and hepatic involvement, and certain drugs could be involved in the pathophysiology of vitamin D deficiency in rheumatological disorders.¹⁵

To our knowledge, vitamin D levels have not been previously studied in Behcet's Disease. The aim of this study was to characterize the vitamin D status of patients

with Behcet's Disease and the relationship between vitamin D levels and the inflammatory process.

MATERIALS AND METHODS

The diagnostic criteria for Behcet's Disease proposed by the International Study Group for Behcet's Disease were used for diagnosis.¹⁶ Thirty-two patients with Behcet's Disease and thirty-one matched healthy controls were included in the study. All participants were informed of the study protocol, and their written informed consent was obtained according to the Declaration of Helsinki. The study was approved by the local ethics committee of Ataturk University.

Subjects in the patient and control groups with a history of liver and kidney diseases, diabetes mellitus, familial hypercholesterolemia, thyroid and parathyroid diseases, and malignancy were excluded from the study. Individuals with osteoporosis or a history of osteoporosis treatment, liver and kidney diseases, endocrine diseases, and post-menopausal women were excluded from the study.

In the study group, three patients were on active phase of the disease. Twenty-seven of the patients were under colchicine therapy at doses of 1 to 1.5 mg/day, and two patients were taking colchicine along with low-dose steroids. Three patients had a history of steroid use.

The heights and weights of all subjects were recorded, and body mass index (BMI) was calculated as weight (kg)/height (m²). Laboratory testing of serum calcium (Ca), phosphate (P), total alkaline phosphatase (ALP), and 25-hydroxyvitamin D levels was conducted for all patients and control subjects. The erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level were determined in whole blood and serum aliquots, respectively. ESR was determined according to the Westergren method and CRP by a nephelometric method (Beckman Array Protein System, USA). 25-hydroxyvitamin D levels were determined in an E-170 ECL system (Roche, Japan) with an electrochemiluminescence method.

Statistical Analysis

Statistical analysis was performed with PASW Statistics 18 (SPSS Inc., Chicago, U.S.A.) for Windows. Statistical analyses were performed using the Mann-Whitney U test. A p value of less than 0.05 was accepted as statistically significant. Correlations among parameters were analyzed using Pearson's correlation coefficient. A multivariable regression model was established to evaluate the effects of different variables on vitamin D levels.

RESULTS

Table I lists the clinical and demographic characteristics of the patient and control groups. The findings are expressed as median (min-max). The demographic and BMI values were similar between groups. The acute-phase reactant levels of ESR and CRP were significantly higher in patients with Behcet's Disease than in the control subjects (p<0.05).

After the data were weighted by age, vitamin D levels were significantly lower in the patient group than in the control group (p<0.001). There was no significant difference between the patients and the controls in terms of Ca, P, or ALP levels (p>0.05). There was no correlation between vitamin D levels and age, BMI, disease duration, ESR, or

Table I - Clinical and laboratory features of patients with Behcet's Disease and healthy controls.

	Patient group	Control group	p-value
Sex (male/female)	14/18	11/20	ns
Age (years)	29 (18-50)	33 (21-57)	ns
Disease duration (months)	33 (3-216)	-	
Height (cm)	164.5 (143-183)	162 (150-182)	ns
Weight (kg)	65.5 (43-92)	66 (50-95)	ns
BMI (kg/m ²)	24.7 (16.8-30.5)	25.4 (19.5-33.5)	ns
Pathergy test positivity (%)	14 (43.8 %)	-	
ESR (mm/h)	13.5 (1-89)	10 (2-25)	p<0.05
CRP (mg/L)	0.5 (0.3-12.6)	0.3 (0.3-1.1)	p<0.05
Ca (mg/dl)	9.4 (8.1-10.5)	9.4 (8.5-10.6)	ns
P (mg/dl)	3.5 (2.6-5.3)	3.5 (2.7-5.3)	ns
ALP (U/L)	84 (38-167)	76 (42-141)	ns
25-hydroxyvitamin D (ng/ml)	13.76 (4-35.79)	18.97 (12.05-36.94)	p<0.001

ns: not significant.

CRP levels (Table II). Multivariable regression analysis was performed to determine the main predictors of vitamin D levels (Table III). The variables included in the model were age, smoking, alcohol intake, and use of colchicine and corticosteroid drugs. Age, smoking, alcohol intake, and use of colchicine were found to be the main predictors. Colchicine therapy was found to have the greatest effect on levels of vitamin D (p<0.001). We did not find a significant relationship between the use of steroids and 25-hydroxyvitamin D (p = 0.62).

DISCUSSION

Behcet's Disease is a systemic and immunoinflammatory form of vasculitis with endothelial dysfunction.¹⁷ The inflammation is generally mediated by cytokines derived from Th1 lymphocytes, such as tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), and IL-18.¹⁸ Vitamin D is a hormone that has important roles in calcium homeostasis and bone turnover.¹⁹ There is an increasing interest in the relationship between vitamin D deficiency and a number of autoimmune diseases.¹²

Decreased vitamin D levels have been reported to correlate with increased SLE disease activity.¹⁴ Animal model studies of SLE have shown that some aspects of the disease decreased in severity when vitamin D intake was increased.²⁰ Vitamin D has also been related to disease activity in RA. Values of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D showed significant negative correlations with RA disease activity.^{13,21}

Vitamin D has immunosuppressant properties and has been considered as a therapeutic intervention for several autoimmune diseases.²² In an in vitro study, Do et al.²³ showed

Table II - Correlation between 25-hydroxyvitamin D levels and clinical parameters in patients with Behcet's Disease.

	Median (min-max)	r	p-value
Age (years)	29 (18-50)	0.126	ns
BMI (kg/m ²)	24.7 (16.8-30.5)	0.323	ns
Disease duration (months)	33 (3-216)	0.303	ns
ESR (mm/h)	13.5 (1-89)	0.258	ns
CRP (mg/L)	0.5 (0.3-12.6)	0.244	ns

ns: not significant.

Table III - Multivariate regression analysis of vitamin D levels with demographic and clinical parameters in patients with Behçet's Disease.

Model	B	Std. error	t	p-value
Constant	22.787	1.065	21.404	p<0.001
Age	-0.064	0.023	-2.855	p<0.01
Smoking	1.179	0.121	9.743	p<0.001
Alcohol intake	1.196	0.298	4.010	p<0.001
Colchicine therapy	-5.101	0.357	-14.304	p<0.001
Corticosteroid therapy	-0.174	0.346	-0.504	ns

ns: not significant.

that vitamin D suppressed the expression of Toll-like receptor (TLR) in monocytes of patients with Behçet's Disease. They also reported that vitamin D may be useful as a therapeutic option for inflammation triggered through TLR2 and TLR4, which are important in the pathogenesis of Behçet's Disease.

In this study, we demonstrated that serum 25-hydroxyvitamin D levels were lower in patients with Behçet's Disease than in the control subjects. To our knowledge, serum 25-hydroxyvitamin D levels have not previously been investigated in patients with Behçet's Disease.

The pathogenesis of vitamin D deficiency is not clearly understood. Several factors, such as impaired calcium and vitamin D intake, malnutrition, smoking, alcohol consumption, inadequate sunlight exposure, hypogonadism, aging, corticosteroid therapy, and impaired physical activity, may play an important roles in the etiopathogenesis of vitamin D deficiency. Increased metabolism or impaired 25-hydroxylation induced by medication or by disease involvement may affect vitamin D values.²⁴ In addition, the inhibition of 1- α -hydroxylase by TNF- α may contribute to lower vitamin D levels.²⁵

In this study, we found that age, smoking, alcohol intake, and use of colchicine were the main predictors of 25-hydroxyvitamin D levels. Colchicine treatment was the most effective predictor of 25-hydroxyvitamin D values. The effects of colchicine on 25-hydroxyvitamin D levels have not yet been fully defined in the literature.

This study had several limitations. First, the number of patients was small. Second, most of the patients were using colchicine, and it is not known whether colchicine affects 25-hydroxyvitamin D levels. Thus, it would be optimal to measure 25-hydroxyvitamin D concentrations before colchicine use. Third, although we did not find a significant relationship between the use of steroids and 25-hydroxyvitamin D, the number of subjects using corticosteroids was small, which may have affected the results. Fourth, serum parathyroid hormone (PTH) levels, calcium intake, physical activity, and sun exposure were not analyzed.

In conclusion, serum 25-hydroxyvitamin D levels are decreased in patients with Behçet's Disease. Smoking, alcohol intake, and use of colchicine are predictive of low 25-hydroxyvitamin D levels. Future interventional studies are needed to determine the efficacy of 25-hydroxyvitamin D in patients with Behçet's Disease.

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REFERENCES

- Kirnap M, Calis M, Kaya N, Muhtaroglu S. Is the Behçet's disease a risk factor for osteoporosis and is relation to cytokines? Bratisl Lek Listy. 2010;111:340-4.
- Erdem FH, Karatay S, Yildirim K, Kiziltunc A. Evaluation of serum paraoxonase and arylesterase activities in ankylosing spondylitis patients. Clinics. 2010;65:175-9, doi: 10.1590/S1807-59322010000200009.
- Hirohata S. Histopathology of central nervous system lesions in Behçet's disease. J Neurol Sci. 2008;267:41-7, doi: 10.1016/j.jns.2007.09.041.
- Zierhut M, Mizuki N, Ohno S, Inoko H, Gül A, Onoé K, et al. Immunology and functional genomics of Behçet's disease. Cell Mol Life Sci. 2003;60:1903-22, doi: 10.1007/s00181-003-2333-3.
- Shang YB, Zhai N, Li JP, Han SX, Ren QS, Song FJ, et al. Study on association between polymorphism of HLA-DRB1 alleles and Behçet's disease. J Eur Acad Dermatol Venereol. 2009;23:1419-22, doi: 10.1111/j.1468-3083.2009.03335.x.
- Mizuki N, Ota M, Katsuyama Y, Yabuki K, Ando H, Shiina T, et al. HLA-B*51 allele analysis by the PCR-SBT method and a strong association of HLA-B*5101 with Japanese patients with Behçet's disease. Tissue Antigens. 2001;58:181-4, doi: 10.1034/j.1399-0039.2001.580306.x.
- Lehmann B, Meurer M. Vitamin D metabolism. Dermatol Ther. 2010;23:2-12, doi: 10.1111/j.1529-8019.2009.01286.x.
- Hamilton B. Vitamin D and human skeletal muscle. Scand J Med Sci Sports. 2010;20:182-90.
- Michos ED, Melamed ML. Vitamin D and cardiovascular disease risk. Curr Opin Clin Nutr Metab Care. 2008;11:7-12, doi: 10.1097/MCO.0b013e3282f2f4dd.
- Ali MM, Vaidya V. Vitamin D and cancer. J Cancer Res Ther. 2007;3:225-30, doi: 10.4103/0973-1482.38998.
- Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers South Med J. 2005;98:1024-7, doi: 10.1097/01.SMJ.0000140865.32054.DB.
- Szodoray P, Nakken B, Gaal J, Jonsson R, Szegedi A, Zold E, et al. The complex role of vitamin D in autoimmune diseases. Scand J Immunol. 2008;68:261-9, doi: 10.1111/j.1365-3083.2008.02127.x.
- Cutolo M, Otsa K, Uprus M, Paolino S, Serio B. Vitamin D in rheumatoid arthritis. Autoimmun Rev. 2007;7:59-64, doi: 10.1016/j.autrev.2007.07.001.
- Thudi A, Yin S, Wandstrat AE, Li QZ, Olsen NJ. Vitamin D levels and disease status in Texas patients with systemic lupus erythematosus. Am J Med Sci. 2008;335:99-104, doi: 10.1097/MAJ.0b013e318134eeb6.
- Khazai N, Judd SE, Tangpricha V. Calcium and vitamin D: skeletal and extraskeletal health. Curr Rheumatol Rep. 2008;10:110-7, doi: 10.1007/s11926-008-0020-y.
- Criteria for diagnosis of Behçet's disease. International Study Group for Behçet's Disease Lancet. 1990;335:1078-80.
- Mendes D, Correia M, Barbedo M, Vaio T, Mota M, Gonçalves O, et al. Behçet's disease—a contemporary review. J Autoimmun. 2009;32:178-88, doi: 10.1016/j.jaut.2009.02.011.
- Oztas MO, Onder M, Gurer MA, Bukan N, Sancak B. Serum interleukin 18 and tumour necrosis factor-alpha levels are increased in Behçet's disease. Clin Exp Dermatol. 2005;30:61-3, doi: 10.1111/j.1365-2230.2004.01684.x.
- Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr. 2003;89:552-72, doi: 10.1079/BJN2003837.
- Abe J, Nakamura K, Takita Y, Nakano T, Irie H, Nishii Y. Prevention of immunological disorders in MRL/l mice by a new synthetic analogue of vitamin D3: 22-oxa-1 alpha,25-dihydroxyvitamin D3. J Nutr Sci Vitaminol (Tokyo). 1990;36:21-31.
- Turhanoglu AD, Güler H, Yönden Z, Aslan F, Mansuroglu A, Ozer C. The relationship between vitamin D and disease activity and functional health status in rheumatoid arthritis. Rheumatol Int DOI: 10.1007/s00296-010-1393-6.
- Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis. 2007;66:1137-42, doi: 10.1136/ard.2007.069831.
- Do JE, Kwon SY, Park S, Lee ES. Effects of vitamin D on expression of Toll-like receptors of monocytes from patients with Behçet's disease. Rheumatology (Oxford). 2008;47:840-8, doi: 10.1093/rheumatology/ken109.
- Borba VZ, Vieira JG, Kasamatsu T, Radominski SC, Sato EI, Lazaretti-Castro M. Vitamin D deficiency in patients with active systemic lupus erythematosus. Osteoporos Int. 2009;20:427-33, doi: 10.1007/s00198-008-0676-1.
- Overbergh L, Decallonne B, Valckx D, Verstuyf A, Depovere J, Laureys J, et al. Identification and immune regulation of 25-hydroxyvitamin D-1-alpha-hydroxylase in murine macrophages. Clin Exp Immunol. 2000;120:139-46, doi: 10.1046/j.1365-2249.2000.01204.x.