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Vitamin D Levels in Takayasu's Arteritis and a Review of the Literature on Vasculitides

Fatma Alibaz-Oner,[1]* Özlem Asmaz-Haliloglu,[2] Dilek Gogas-Yavuz,[3] Meryem Can,[1] Goncagul Haklar,[4] and Haner Direskeneli[1]

[1]*Department of Rheumatology, School of Medicine, Marmara University, Istanbul, Turkey*
[2]*Department of Internal Medicine, School of Medicine, Marmara University, Istanbul, Turkey*
[3]*Department of Endocrinology, School of Medicine, Marmara University, Istanbul, Turkey*
[4]*Department of Biochemistry, School of Medicine, Marmara University, Istanbul, Turkey*

Objective: Takayasu's arteritis (TAK) is a chronic, large-vessel vasculitis. Vitamin D, as a steroidal hormone, has recently been shown to have immunoregulatory and immunosuppressive effects. Low vitamin D levels are demonstrated in various autoimmune disorders. The aim of this study is to investigate vitamin D levels in patients with TAK. A comprehensive review of vitamin D levels in systemic vasculitides (SVs) is also performed. *Methods:* The study included 36 patients with TAK, 28 patients with Behçet's disease (BD) as disease control and 30 sex-matched healthy controls. Plasma 25-hydroxy vitamin D (25(OH) vit D) levels were measured with high-performance liquid chromatography. "Deficiency" was defined as 25(OH) vit D levels below 25 nmol/l and "insufficiency" as below 50 nmol/l. *Results:* Plasma 25(OH) vit D levels were significantly lower in TAK patients (16.93 ± 10.62 nmol/l) than healthy controls (64.63 ± 21.82 nmol/l). Vitamin D level in BD patients (38.8 ± 20.9 nmol/l) is lower than healthy controls but higher than TAK patients. The frequency of vitamin D deficiency was 83.3% in patients with TAK compared to 3.3% in healthy controls. Plasma 25(OH) vit D levels were same between clinically active and inactive patients. In literature review, very few studies were found to investigate vitamin D in SVs. *Conclusion:* We observed a high prevalence of vitamin D deficiency in patients with TAK. As various immune effects of vitamin D on mononuclear cells and arterial endothelium is shown, vitamin D deficiency can be a predisposing factor for immune activation in SV. We therefore suggest monitorization and replacement of vitamin D status in all TAK and other SV patients. J. Clin. Lab. Anal. **30**:529–533, 2016. © 2015 Wiley Periodicals, Inc.

Key words: Takayasu's arteritis; vitamin D deficiency; vasculitis

BACKGROUND

Takayasu's arteritis (TAK) is a rare, chronic, large-vessel vasculitis that predominantly affects aorta, its major branches, and the pulmonary arteries (1). Various signs and symptoms such as constitutional features (fever, malaise, anorexia, weight loss), extremity pain, claudication, light headedness, bruits, absent or diminished pulses, and loss of blood pressure can be present according to the vessel involvement (2). The etiology of TAK is still unknown, but infectious agents (3) and genetic factors are implicated (4, 5).

Vitamin D is a steroidal hormone regulating calcium homeostasis, bone formation, and resorption via interaction with parathyroid glands, kidneys, and intestines. Vitamin D shows its biological effect by binding to its intracellular vitamin D receptor (VDR), which is widely distributed in the body, including the cells of the immune system (6). Expression of VDR is shown on monocytes, macrophages, dendritic cells, NK cells, and T and B lymphocytes. With various effects on cell proliferation and

*Correspondence to: Fatma Alibaz-Oner, Department of Rheumatology, School of Medicine, Marmara University, Fevzi Çakmak Mahallesi 1121, sokak No. 14, 34200 Esenler, Istanbul, Turkey. E-mail: falibaz@gmail.com

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differentiation, vitamin D is a potential candidate for immune system regulation (7).

Vitamin D deficiency is very common in patients with various autoimmune and other chronic diseases including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and type 2 diabetes (T2DM) (8–10). However, studies are very limited in systemic vasculitides (SVs). The aim of this study is to investigate vitamin D levels in patients with TAK. We also performed a comprehensive review of the literature on vitamin D in SVs.

METHODS

The study included 36 patients (age: 40.83 ± 11.57 years, F/M: 33/3) with TAK, 28 (42.1 ± 9.8, F/M: 24/4) patients with Behçet's disease (BD) as disease control, and 30 age- and sex-matched healthy control subjects (age: 38.67 ± 7.35 years, F/M: 27/3) between February 2012 and May 2012. Patients with TAK fulfilled the criteria of American College of Rheumatology (ACR) (11). According to the angiographic classification, 47.2% of the study group had type I disease, 47.2% had type V disease, 2.7% had type IV disease, and 2.7% had type IIb disease (12). Refractory disease for TAK is defined as recently published by the Turkish Takayasu Group, "angiographic or clinical progression despite treatment" or any of the following characteristics: corticosteroid dose >7.5 mg/day after 6 months of treatment despite the administration of conventional immunosuppresives (methotrexate, azathioprine, leflunomide, or cyclophosphamide), new surgery due to persistent disease activity, frequent attacks (>3/year), or mortality associated with disease activity (4). Thirty-two patients (88.8%) were on oral methyl-prednisolone therapy. As additional immunosuppression, 20 (55.6%) patients were on azathioprine, 12 (33.3%) were on methotrexate, and 1 (8.3%) were on leflunomide therapy.

After collecting blood samples, plasma 25-hydroxy vitamin D (25(OH) vit D) levels were measured with high-performance liquid chromatography (HPLC; Spectra System, GmbH, Munich, Germany). According to the reference range of the test kit, "deficiency" was defined as 25(OH) vit D level below 25 nmol/l and "insufficiency" as below 50 nmol/l, and the recommended level of 25(OH) vit D was above 100 nmol/l (13). The study was performed according to the Declaration of Helsinki. All subjects gave informed consent before participation.

Statistical data were performed with Statistical Package for the Social Sciences 16.0 (SPSS, Chicago, IL) program. Results were expressed as means and standard deviations. The independent samples *t*-test and chi-square test were used for comparisons of data. Pearson correlation test was used for analyzing correlations.

The literature search for vitamin D in vasculitis was performed with keywords "vitamin D" and "vasculitis" in PubMed, and 52 references were found. A cross-check was also done with keywords for each specific vasculitis, namely, leucocytoclastic vasculitis, Henoch–Schonlein purpura, polyarteritis nodosa, Wegener's granulomatosis Granulomatosis with Polyangitis (GPA), Churg–Strauss syndrome Eosinophilic granulomatosis with polyangiitis (EPA), TAK, giant-cell arteritis, BD, and Kawasaki's disease. When case reports, reviews, and studies on vitamin D replacement for corticosteroid-induced osteoporosis were excluded from the analysis, 16 studies were selected for further review.

RESULTS

The mean disease duration of TAK patients was 5.37 ± 4.9 years. Mean erythrocyte sedimentation rate was 23.31 ± 16.24 mm/h, mean C-reactive protein level was 8.41 ± 12.27 mg/l. Plasma 25(OH) vit D were significantly lower in TAK patients (16.93 ± 10.62 nmol/l) compared to healthy controls (64.63 ± 21.82 nmol/l; $P = 0.001$; Fig. 1). The frequency of vitamin D deficiency was 83.3% ($n = 30$) in patients with TAK versus 3.3% ($n = 1$) in healthy controls ($P = 0.001$). Plasma 25(OH) vit D were significantly lower in BD patients (38.8 ± 20.9 nmol/l) compared to healthy controls (64.63 ± 21.82 nmol/l; $P = 0.001$), but higher than patients with TAK ($P<0.001$ for both). The frequency of vitamin D deficiency was 46.5% ($n = 13$) in patients with BD. This rate is higher than healthy controls but lower than TAK ($P < 0.001$ for both).

Serum calcium, phosphate, parathyroid hormone, and alkalene phosphatase levels of all patients and healthy controls were in normal ranges. Ten (27.8%) patients with TAK were clinically active according to physician's global assessment. Plasma 25(OH) vit D levels were similar between active and inactive patients ($P = 0.75$). Similarly, there was no significant difference between male ($n = 3$, 100%) and female ($n = 27$, 81%) patients in terms of vitamin D deficiency. No association was present between vitamin D levels and acute-phase reactants. Similarly, no effect of treatment or disease subtypes on vitamin D levels was observed. No differences were also present between the subgroups of patients with TAK according to age of onset, presence of surgery, or refractory disease (Table 1). Twelve (33.3%) patients were taking oral calcium carbonate (1,200 mg/day) and oral vitamin D3 (400 IU/day). No difference was also present between the patients taking oral vitamin D replacement or not ($P = 0.89$).

DISCUSSION AND LITERATURE REVIEW

We observed significantly lower serum 25(OH) vit D levels among TAK patients compared to healthy

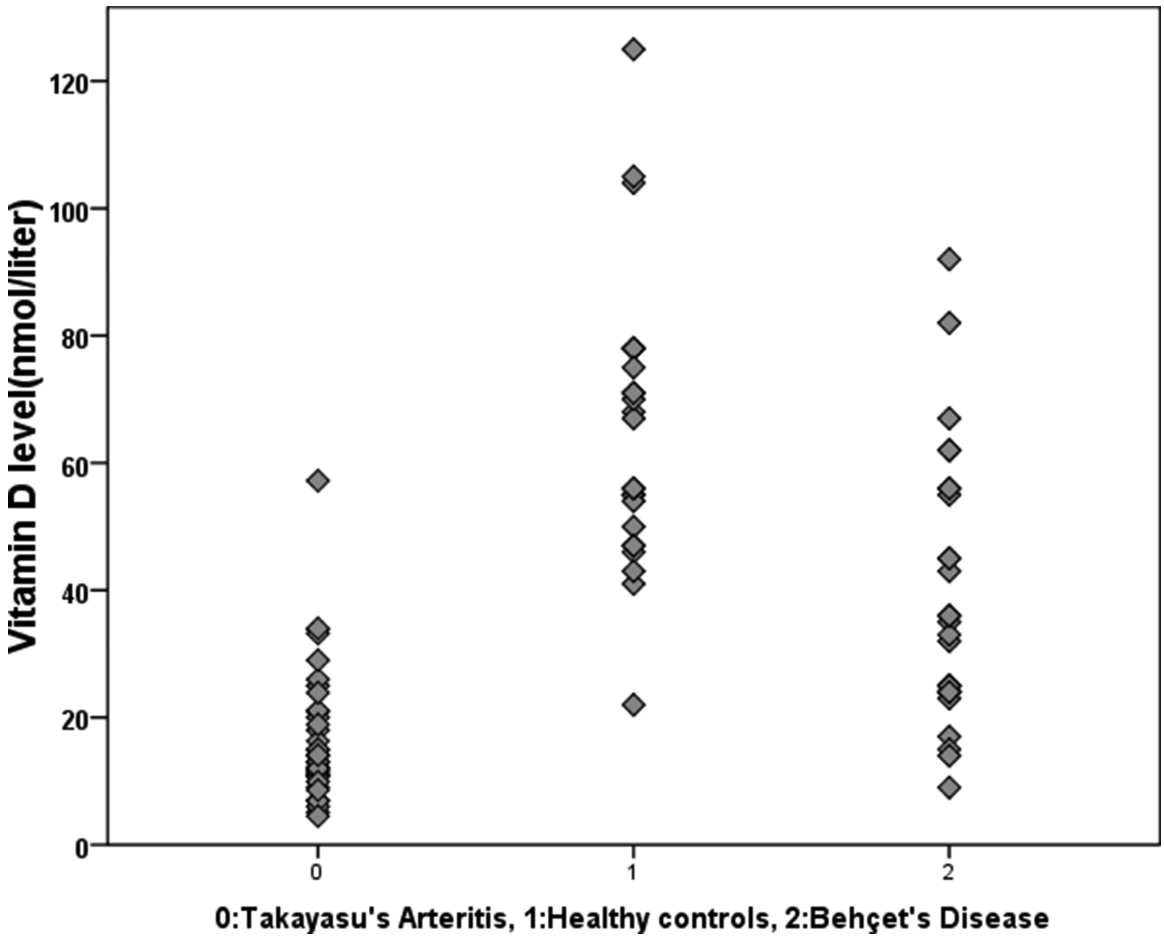

Fig. 1. Vitamin D levels in patients with Takayasu's arteritis, Behçet's disease, and healthy controls.

controls, with a high prevalence of vitamin D deficiency in our study. High prevalence of vitamin D deficiency was reported before also in rheumatological diseases such as BD and ankylosing spondylitis from Turkey, having sunshine along four seasons (14, 15). In the present study, we also found increased vitamin D deficiency in BD. However, to our knowledge, this is the first study that investigates vitamin D levels in patients with TAK.

The etiology of TAK is still unknown, but infectious agents (3, 16) and genetic factors (4, 5) are implicated in the pathogenesis (17, 18). Immunohistochemical studies from the aortic tissue of patients with TAK showed infiltrations by macrophages, T cells ($CD4^+$, $CD8^+$, and $\gamma\delta^+$), NK cells, and neutrophils (19). $CD4^+$ T cells initiate and maintain granuloma formation by releasing interferon-γ (IFNγ) (20), and granulomatous inflammation strongly depends on T-helper type 1 (Th1) and recently described Th17-type immune patterns (21, 22).

$1,25(OH)_2D_3$, the biologically active form of vitamin D, inhibits T lymphocyte proliferation (23, 24), particularly of the Th1 arm (25, 26). Addition of $1,25(OH)_2D_3$ to peripheral blood mononuclear cells (PBMCs) decreases secretion of IL-2 and IFNγ, and upregulates IL-5 and IL-10 production, leading to a Th2-resembling response

TABLE 1. Vitamin D Deficiency in Subgroups of Patients With Takayasu's Arteritis

		Age at onset		Surgery		Refractory disease	
		≤40 ($n = 24$)	>40 ($n = 12$)	Present ($n = 15$)	Not present ($n = 21$)	Refractory ($n = 10$)	Not refractory ($n = 26$)
Vitamin D deficiency	*n*	20	10	13	17	8	22
	%	83.3	83.3	86.6	80.9	80	84.6
P value		0.691		0.507		0.544	

(27). Vitamin D deficiency also leads to an impairment of regulatory T and dendritic cells (28, 29). Addition of $1,25(OH)_2D_3$ was shown to inhibit the expression of IL-6, an important cytokine that stimulates Th17 cells and is upregulated in large-vessel vasculitides. With these data accumulating on its immunosuppressive role, replacement or even supraphysiological doses of vitamin D supplementation is recently suggested for all autoimmune diseases (30, 31).

Although we demonstrated low vitamin D levels in our study, in contrast to some other studies, such as in SLE (32), we observed no association with disease activity or vitamin D replacement. Similar results are also reported in the literature for BD. Still, these results should be interpreted with caution, as our active patient subset was small and replacement therapy is only cross-sectionally questioned in our population.

Limitations of our study were its small sample size, the lack of data regarding sun exposure, use of sunscreen and style of clothing. However, we studied vitamin D levels in winter season (similar to our previous study in BD) (15) when sun exposure was lowest in Istanbul, Turkey, which might decrease the influence of sun exposure to our results.

Literature Review

In the literature review, no study was observed to investigate vitamin D status in patients with large-vessel vasculitides (TAK and giant-cell arteritis). In an early study, Chesney et al. have demonstrated the importance of vitamin D deficiency in children receiving glucocorticoids for diseases including vasculitides (33). In an epidemiological survey and meta-analysis, the incidence of granulomatosis with polyangiitis (Wegener's) and eosinophilic polyangiitis (Churg–Strauss) is shown to be increased with latitude and decreased ambient UV radiation, suggesting a role of vitamin D deficiency in Anti-neutrophil cytoplasmic antibody ANCA-associated vasculitides (AAV) (30). However, no studies on vitamin D levels in AAV are published. Vitamin D levels and associated mechanisms are studied mostly in BD (10, 14, 34–40) Five of these studies demonstrated decreased vitamin D levels in patients with BD, not associated with disease activity (10, 14, 37, 39, 40). In other studies, in vitro modulating effects of vitamin D on toll-like receptor expression of monocytes, number of T-regulatory cells, IFNγ/IL-4 ratio, and Th1/Th17 responses were demonstrated in BD (10, 34, 38). Another study showed ameliorating effects of vitamin D on a Herpes simplex induced Behcet's-like animal model (35) . Association of VDR gene polymorphisms and vitamin D family genes with BD is also demonstrated (36, 41). In the only other study measuring vitamin D levels in vasculitides, Terrier et al. reported that in chronic hepatitis C infection, patients with vitamin D deficiency had more vasculitis, especially purpura and elevated cyroglobulinemia levels (42).

In vitro effects of vitamin D on vascular endothelium are also studied for clarifying vasculitic mechanisms. Active vitamin D is shown to inhibit VCAM-1 and IL-8 expression from human coronary arterial cells (HCAC) (43). Vitamin D also significantly inhibited TNF-α-induced (where TNF is tumor necrosis factor) NF-κB (where NF is nuclear factor) activation and E-selectin expression in HCAC (44) . Similar results are observed in a chronic kidney disease like environment and calcitriol normalized the expression, secretion, and activity of eNOS, RAGE and IL-6 (45). As an implication for clinical effects on vascular endothelium, vitamin D replacement is shown to improve endothelial functions, measured with flow-mediated dilatation, in patients with BD (15).

In conclusion, we observed a high prevalence of vitamin D deficiency in patients with TAK. As vitamin D plays an important role in regulating immune system, vitamin D deficiency can be a predisposing factor for immune activation and we suggest the monitorization of vitamin D status and replacement in TAK patients with vitamin D deficiency. Further studies in other SVs are also necessary.

CONFLICT OF INTEREST

None declared.

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