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T. Yoon[1] · S. S. Ahn[2] · J. Y. Pyo[2] · J. J. Song[2,3] · Y.-B. Park[2,3] · S.-W. Lee[2,3]

[1] Department of Medical Science, BK21 Plus Project, Yonsei University, College of Medicine, Seoul, Korea (Republic of)

[2] Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea (Republic of)

[3] Institute for Immunology and Immunological Diseases, Yonsei University College of Medicine, Seoul, Korea (Republic of)

Serum vitamin D level correlates with disease activity and health-related quality of life in antineutrophil cytoplasmic antibody-associated vasculitis

Supplementary Information

The online version of this article (https://doi.org/10.1007/s00393-020-00949-2) includes supplementary data. Article and supplementary material are available at www.springermedizin.de. Please enter the title of the article in the search field, the supplementary material can be found under "Ergänzende Inhalte".

Introduction

Vitamin D, a fat-soluble vitamin, is known to play a crucial role in the regulation of calcium and phosphate balance and the control of bone formation and resorption [1]. Among the sources of vitamin D, pre-vitamin D2 (ergocalciferol) is obtained from the intake of foods of vegetable origin, whereas pre-vitamin D3 (cholecalciferol) is obtained from the metabolism of 7-dehydrocholesterol in the skin through solar ultraviolet light or from the intake of foods of animal origin. Subsequently, ergocalciferol and cholecalciferol are converted to calcidiol—25-hydroxy vitamin D [25(OH)D]—in the liver. Ultimately, 25(OH)D is metabolised to its active form, calcitriol—1,25 dihydroxy vitamin D [$1,25(OH)_2D$]—in the kidneys [2]. Although vitamin D was primarily identified to play a major role in bone metabolism, evidence has demonstrated that $1,25(OH)_2D$ could modulate the function of immune cells through its nuclear receptor and influence inflammation and immunity [3]. In immune cells, $1,25(OH)_2D$ interacts with nuclear vitamin D receptor (VDR) to produce a complex of $1,25(OH)_2D$–VDR. Consequently, the complex binds to vitamin D response elements in the promoter region of the target genes, thereby modulating the inflammatory process in immune cells, including dendritic cells, B cells and T cells [2, 4]. In this regard, several studies have evaluated the association of vitamin D with clinical features in autoimmune diseases; in addition, the widespread deficiency of vitamin D in patients with autoimmune rheumatic diseases and the inverse correlation between vitamin D level and severity of disease are gradually being recognised [5–7].

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) comprises a group of the systemic vasculitides, which principally involve small-sized vessels, such as capillaries, arterioles and venules, and seldom medium-sized arteries. AAV has three disease subtypes, namely microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA) [8, 9]. Similar to other systemic autoimmune diseases, dendritic cells, macrophages, T cells and B cells play crucial roles in the inflammatory process of AAV [10]. Therefore, it is hypothetically rational to presume that vitamin D is associated with clinical features in AAV. Based on this background, several studies have clarified the clinical implication of vitamin D in patients with AAV, and the most significant relapse rate was observed in the autumn among the four seasons, attributable to a decrease in the serum level of 25(OH)D [11]. On the contrary, Gatenby et al. have demonstrated an association between the incidence rate of AAV and increasing latitude and decreased UV radiation, suggesting the protective immunomodulatory effect of vitamin D [12]. Furthermore, it was revealed that

T. Yoon and S. S. Ahn contributed equally to this work.

patients with AAV exhibited lower serum levels of 25(OH)D3 than healthy controls, similar to patients with other autoimmune rheumatic diseases [13]. However, the association between vitamin D and disease severity in AAV remains unclear. Consequently, this study aimed to determine the levels of two different forms of vitamin D—25(OH)D, which is a sum of 25(OH)D2 and 25(OH)D3, and 25(OH)D3, which only includes 25(OH)D in its D3 form—in the sera of patients with AAV and assess its relationship with disease activity.

Materials and methods

The SHAVE cohort and patients

We included 54 patients with AAV from the Severance Hospital ANCA associated VasculitidEs (SHAVE) cohort who were not on vitamin D supplements. All patients were categorised as patients with AAV at the Division of Rheumatology in Severance Hospital and fulfilled the 1990 American College of Rheumatology (ACR) classification criteria for EGPA, the 2007 European Medicines Agency algorithms for AAV and polyarteritis nodosa (the 2007 EMA algorithm), and the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides (the 2012 CHCC definitions) [8, 9, 14]. In the SHAVE cohort, whole blood was obtained following the provision of informed consent by patients, and the patients were subjected to clinical and laboratory evaluations every 3 to 6 months. Notably, 50 age- and sex-matched healthy individuals who had undergone health screening in the Severance Healthcare Clinic were included as controls. None of the subjects included in the healthy control group were on vitamin D supplements. This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Severance Hospital (4-2016-0901), and written informed consent was obtained from the patients during blood sampling.

Acquisition of clinical and laboratory data

Demographic data included age, sex and disease duration. Similarly, AAV subtypes and ANCA positivity were also investigated by evaluating the medical records. The clinical manifestations were estimated in accordance with the items in BVAS version 3 [15]. In addition, four AAV-specific indices were evaluated in the patients: 36-item Short-form Health Survey (SF-36) physical component summary (PCS) and mental component summary (MCS) scores as a functional index, BVAS version 3 as an activity index, five-factor score as a prognostic index and vasculitis damage index as a damage index [15–18]. Regarding laboratory data, acute-phase reactants comprised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels; in addition, routine laboratory test parameters consisted of white blood cell (WBC) and platelet counts, haemoglobin, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase and total bilirubin. The use of glucocorticoid and immunosuppressive drugs was additionally investigated.

Assessment of seasonal difference and vitamin D level measurement

Seasonal variations in vitamin D levels in the patients were evaluated based on a meteorological definition: Spring (March 1 to May 31), summer (June 1 to August 31), autumn (September 1 to November 30) and winter (December 1 to February 28). In addition, considering the fact that 25(OH)D is more stable than 1,25(OH)D in the sera and is the primary circulating form of vitamin D, two different forms of vitamin D—25(OH)D, which is a sum of 25(OH)D2 and 25(OH)D3, and 25(OH)D3, which only includes 25(OH)D in its D3 form—were measured using the Packard COBRA Quantum Gamma Counter (Packard Instruments, Downers Grove, IL, USA) following the manufacturer's instructions. Notably, vitamin D deficiency was defined as a serum level of 25(OH)D below 20 ng/mL, as previously explained [19].

Statistical analyses

All statistical analyses were performed using the SPSS software (version 25 for Windows; IBM Corp., Armonk, NY, USA). Continuous and categorical variables were presented as median (interquartile range) and numbers (percentage), respectively. Significant differences in the categorical variables were determined using the chi-squared test; continuous variables were compared using the Kruskal–Wallis or the Mann–Whitney U test. The correlation coefficient between the continuous variables was acquired using Spearman correlation analysis. In addition, the relationship between continuous variables was examined using linear regression analysis. Multivariable analysis was performed by the forward stepwise method using variables with statistical significance from the univariable analysis. Notably, p-values less than 0.05 were considered statistically significant.

Results

Characteristics of patients with AAV

The characteristics of the 54 patients with AAV are described in **Table 1**. The median age was 61.5 years and 19 (35.2%) patients were men. Thirty-two, 10 and 12 patients were categorised as having MPA, GPA and EGPA, respectively. For ANCA types, myeloperoxidase ANCA or perinuclear ANCA was detected in more than 60% of the patients, with pulmonary involvement being the most common (68.5%) clinical manifestation, followed by renal and otorhinolaryngologic manifestations. The median serum levels of 25(OH)D and 25(OH)D3 in the patients were 15.7 ng/mL and 16.0 ng/mL, respectively. Most frequently, 57.4% and 22.2% of patients were actively on glucocorticoid and cyclophosphamide treatments, respectively.

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Serum vitamin D level correlates with disease activity and health-related quality of life in antineutrophil cytoplasmic antibody-associated vasculitis

Abstract

Background and objective. The association between vitamin D levels and disease activity has been established in patients with several autoimmune rheumatic diseases. We aimed to examine the association between vitamin D and disease activity of antineutrophil cytoplasmic antibody-associated vasculitis (AAV).

Methods. Fifty-four AAV patients and 50 age- and sex-matched healthy controls without vitamin D supplements were included. Clinical and laboratory data were evaluated during the assessment of vitamin D levels. Two different forms of vitamin D in the sera—25(OH)D, which is the sum of 25(OH)D2 and 25(OH)D3, and 25(OH)D3, which only includes 25(OH)D in its D3 form—were measured, and the relationship between vitamin D and the obtained data was assessed. Variations in vitamin D levels relative to the season were also evaluated.

Results. Patients with AAV demonstrated considerably lower 25(OH)D serum levels than healthy controls (16.0 vs. 20.4 ng/mL, $p = 0.016$), and the proportion of individuals with vitamin D deficiency was higher in patients with AAV than in healthy controls (68.5% vs. 48.0%, $p = 0.035$). Both serum 25(OH)D and 25(OH)D3 were positively associated with the 36-item Short-form Health Survey (SF-36) physical component summary and SF-36 mental component summary (MCS) scores. A negative correlation was observed between 25(OH)D and 25(OH)D3 serum levels and Birmingham vasculitis activity score (BVAS), C-reactive protein (CRP), and white blood cell count. Linear regression analysis indicated haemoglobin and 25(OH)D levels to be independently associated with BVAS and CRP and 25(OH)D levels with SF-36 MCS score. No seasonal variations were observed in vitamin D levels.

Conclusion. The results from this study suggest that vitamin D levels could provide clinically useful information in AAV.

Keywords

Calcidiol · ANCA-associated vasculitides · Biomarker · 36-item short-form health survery · Birmingham vasculitis activity score

Serum-Vitamin-D-Spiegel korreliert mit Krankheitsaktivität und gesundheitsbezogener Lebensqualität bei antineutrophile-zytoplasmatische-Antikörper-assoziierter Vaskulitis

Zusammenfassung

Hintergrund und Ziel. Der Zusammenhang zwischen dem Vitamin-D-Spiegel und der Krankheitsaktivität ist bei Patienten mit verschiedenen rheumatischen Autoimmunerkrankungen nachgewiesen worden. Ziel der Studie war es, den Zusammenhang zwischen Vitamin-D-Spiegel und Krankheitsaktivität bei der antineutrophile-zytoplasmatische-Antikörper-assoziierten Vaskulitis (AAV) zu untersuchen.

Methoden. In die Studie wurden 54 AAV-Patienten und 50 in Alter und Geschlecht damit übereinstimmende gesunde Kontrollen ohne Vitamin-D-Substitution einbezogen. Bei der Untersuchung der Vitamin-D-Spiegel wurden auch klinische und weitere Labordaten erhoben. Es wurden 2 verschiedene Formen von Vitamin D im Serum gemessen – 25(OH)D, welches 25(OH)D2 und 25(OH)D3 umfasst, und 25(OH)D3, welches nur das 25(OH)D in seiner D3-Form einschließt, – und der Zusammenhang zwischen Vitamin D und den ermittelten Daten beurteilt. Auch Schwankungen bei den Vitamin-D-Spiegeln in Abhängigkeit von der Jahreszeit wurden untersucht.

Ergebnisse. Patienten mit AAV wiesen deutlich geringere 25(OH)D-Spiegel im Serum auf als gesunde Kontrollen (16,0 vs. 20,4 ng/ml; $p = 0{,}016$), und der Anteil von Personen mit Vitamin-D-Mangel war bei AAV-Patienten höher als bei gesunden Kontrollen (68,5 vs. 48,0%; $p = 0{,}035$). Sowohl Serum-25(OH)D als auch -25(OH)D3 waren positiv mit dem Score der zusammengefassten körperlichen Komponente des 36-Item Short-Form Health Survey (SF-36) und der zusammengefassten psychischen Komponente (MCS) des SF-36 korreliert. Eine negative Korrelation fand sich zwischen den Serumwerten für 25(OH)D und 25(OH)D3 sowie dem Birmingham Vasculitis Activity Score (BVAS), C-reaktivem Protein (CRP) und der Leukozytenzahl. Die lineare Regressionsanalyse zeigte, dass Hämoglobin- sowie 25(OH)D-Spiegel in unabhängiger Weise mit dem BVAS und CRP sowie 25(OH)D-Spiegel mit dem SF-36-MCS-Score korreliert waren. Jahreszeitliche Schwankungen wurden nicht beim Vitamin-D-Spiegel festgestellt.

Schlussfolgerung. Den Ergebnissen der vorliegenden Studie zufolge könnte der Vitamin-D-Spiegel klinisch nützliche Informationen bei AAV liefern.

Schlüsselwörter

Calcidiol · ANCA-assoziierte Vaskulitis · Biomarker · 36-Item Short-Form Health Survery · Birmingham Vasculitis Activity Score

Comparison of 25(OH)D between patients with AAV and controls, and vitamin D levels in patients with AAV according to the presence of renal involvement

Patients with AAV demonstrated a considerably lower level of 25(OH)D than healthy controls (median 16.0 vs. 20.4 ng/mL, $p = 0.016$; **Fig. 1a**), and the proportion of patients with vitamin D deficiency (<20 ng/mL) was substantially higher in patients with AAV than in healthy controls: 68.5% (37/54) vs. 48.0% (24/50), $p = 0.035$ (**Fig. 1b**).

Since vitamin D is known to be reduced in patients with kidney diseases [20], differences in 25(OH)D and 25(OH)D3 were compared among patients with AAV with and without renal involvement. However, no difference was observed in the serum levels of 25(OH)D and 25(OH)D3 among AAV patients with and without renal involvement (**Fig. 1c, d**).

Table 1 Clinical and laboratory characteristics of 54 patients with AAV

Variables	Values
Demographics	
Age (years)	61.5 (21.3)
Male sex, *N*, (%)	19 (35.2)
Disease duration (days)	21.5 (132.0)
AAV subtypes, N (%)	
MPA	32 (59.3)
GPA	10 (18.5)
EGPA	12 (22.2)
ANCA types, N (%)	
MPO-ANCA positivity	31 (57.4)
P-ANCA positivity	33 (61.1)
PR3-ANCA positivity	3 (5.6)
C-ANCA positivity	4 (7.4)
Clinical manifestations, N, (%)	
General	23 (42.6)
Cutaneous	7 (13.0)
Mucous/eye	4 (7.4)
Otorhinolaryngologic	24 (44.4)
Pulmonary	37 (68.5)
Cardiovascular	4 (7.4)
Abdominal	0 (0)
Renal	29 (53.7)
Nervous	10 (18.5)
AAV-specific indices	
SF-36 PCS	47.5 (33.4)
SF-36 MCS	55.7 (37.7)
FFS	1.0 (1.0)
BVAS	10.0 (12.0)
VDI	3.0 (2.0)
Acute phase reactants	
ESR (mm/hr)	37.0 (46.8)
CRP (mg/L)	3.0 (19.4)
Routine laboratory tests	
WBC count (/mm^3)	7705.0 (4,600.0)
Haemoglobin (g/dL)	11.0 (4.7)
Platelet count (× 1000/mm^3)	295.0 (162.3)
Blood urea nitrogen (mg/dL)	19.9 (22.9)
Creatinine (mg/dL)	0.9 (1.8)
AST (IU/L)	18.5 (9.3)
ALT (IU/L)	19.0 (13.5)
Total bilirubin (mg/dL)	0.5 (0.4)
Serum vitamin D concentration	
Serum 25(OH)D (ng/mL)	16.0 (11.9)
Serum 25(OH)D3 (ng/mL)	15.7 (13.6)
Current medications, N (%)	
Glucocorticoid	31 (57.4)
Cyclophosphamide	12 (22.2)
Rituximab	1 (1.9)
Azathioprine	4 (7.4)
Mycophenolate mofetil	1 (1.9)
Tacrolimus	2 (3.7)
Methotrexate	2 (3.7)

Values are expressed as median (interquartile ranges) or number (percentage)
AAV antineutrophil cytoplasmic antibody-associated vasculitis, *MPA* microscopic polyangiitis, *GPA* granulomatosis with polyangiitis, *EGPA* eosinophilic GPA, *ANCA* antineutrophil cytoplasmic antibody, *MPO* myeloperoxidase, *P* perinuclear, *PR3* proteinase 3, *C* cytoplasmic, *SF-36* Short-Form 36-item Health Survey, *PCS* physical component summary, *MCS* mental component summary, *FFS* five-factor score, *BVAS* Birmingham Vasculitis Activity Score, *VDI* vasculitis damage index, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *WBC* white blood cell, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *25(OH)D* 25-hydroxy vitamin D, *25(OH)D3* 25-hydroxy vitamin D3

Correlation analysis of 25(OH)D and 25(OH)D3 with continuous variables

Among the continuous variables included, both serum 25(OH)D and 25(OH)D3 were positively correlated with SF-36 PCS ($r = 0.310$, $p = 0.023$ and $r = 0.314$, $p = 0.021$, respectively) and SF-36 MCS ($r = 0.369$, $p = 0.006$ and $r = 0.365$, $p = 0.007$, respectively) scores. By contrast, a negative correlation was observed between the serum levels of 25(OH)D and 25(OH)D3 with BVAS ($r = -0.313$, $p = 0.021$ and $r = -0.327$, $p = 0.016$, respectively), CRP level ($r = -0.312$, $p = 0.022$ and $r = -0.317$, $p = 0.019$, respectively), and WBC count ($r = -0.297$, $p = 0.029$ and $r = -0.283$, $p = 0.038$, respectively; Tab. S1 in the electronic supplementary material online).

Linear regression analysis of continuous variables

In the assessment of the factors related to BVAS by linear regression analysis, ESR, CRP, haemoglobin, blood urea nitrogen, creatinine and 25(OH)D were seemingly related to BVAS. However, the multivariable analysis demonstrated an independent association between haemoglobin and 25(OH)D level with BVAS following adjustment (**Table 2**). On the contrary, when 25(OH)D was set as a dependent variable, the relationship between 25(OH)D and BVAS was exclusively evident in the adjusted analysis (Tab. S2).

Regarding SF-36 scores, an association between SF-36 PCS and ESR, CRP, WBC count, haemoglobin and 25(OH)D was observed in univariable analysis; however, the multivariable analysis indicated that only CRP level was significantly associated with SF-36 PCS score (Tab. S3). On the contrary, SF-36 MCS was associated with ESR, CRP, WBC count and 25(OH)D level in the univariable analysis, and an independent association was observed between CRP and 25(OH)D levels in the multivariable analysis (**Table 2**).

Seasonal variation in the level of vitamin D

Because serum vitamin D could be influenced by seasonal variations, the difference in the levels of 25(OH)D and 25(OH)D3 were compared among patients based on the season. However, following the classification of patients based on their assessment period into four seasons (spring, summer, autumn and winter), no difference was observed in the serum levels of 25(OH)D and 25(OH)D3 (**Fig. 2a, b**).

Discussion

This study revealed that the serum level of 25(OH)D was considerably lower in patients with AAV than in healthy controls; this is consistent with the observations of Kalsch and colleagues [13]. In addition, deficiency in vitamin D, i.e., 25(OH)D <20 ng/mL, was predominant in patients with AAV compared to controls (68.5% vs. 48.0%, $p = 0.035$). Similarly, it was observed that serum 25(OH)D and 25(OH)D3 were associated with the disease activity of AAV and the PCS and MCS scores of SF-36, which is an extensively used measure in the evaluation of health-related quality of life (HRQoL). Linear regression analysis indicated an independent association

Table 2 Univariable and multivariable linear regression analysis of continuous variables with BVAS and SF-36 MCS

Linear regression analysis with BVAS						
	Univariable analysis			**Multivariable analysis**		
Variables[a]	**β**	**95% CI**	***P*-value**	**β**	**95% CI**	***P*-value**
ESR	0.073	0.021, 0.125	0.007	–	–	–
CRP	0.054	0.012, 0.096	0.012	–	–	–
Haemoglobin	−1.591	−2.201, −0.980	<0.001	−1.494	−2.094, −0.894	<0.001
Blood urea nitrogen	0.177	0.082, 0.273	<0.001	–	–	–
Creatinine	1.352	0.406, 2.298	0.006	–	–	–
25(OH)D	−0.228	−0.421, −0.036	0.021	−0.165	−0.326, −0.003	0.046
Linear regression analysis with SF-36 MCS						
	Univariable analysis			**Multivariable analysis**		
Variables[b]	**β**	**95% CI**	***P*-value**	**β**	**95% CI**	***P*-value**
ESR	−0.232	−0.389, −0.075	0.005	–	–	–
CRP	−0.186	−0.311, −0.060	0.004	−0.144	−0.271, −0.016	0.028
WBC count	−1.665	−2.854, −0.475	0.007	–	–	–
25(OH)D	0.817	0.245, 1.390	0.006	0.614	0.033, 1.194	0.039

BVAS Birmingham Vasculitis Activity Score, *SF-36* Short-Form 36-item Health Survey, *MCS* mental component summary, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *25(OH)D* 25-hydroxy vitamin D, *WBC* white blood cell, *CI* confidence interval

[a]Variables of age, WBC, platelet count, aspartate aminotransferase, alanine aminotransferase and total bilirubin were also included but statistical significance was not present in univariable analysis

[b]Variables of age, BVAS, haemoglobin, platelet count, blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase and total bilirubin were also included but statistical significance was not present in univariable analysis

between 25(OH)D and BVAS and SF-36 MCS score, suggesting that measuring vitamin D levels could provide clinically useful information in AAV.

Several experimental studies suggest a close relationship between vitamin D and autoimmune diseases through the exertion of anti-inflammatory properties. First, regarding dendritic cells, active vitamin D could hinder the differentiation and maturation of dendritic cells while promoting the immune-tolerogenic function, which could result in reductions in interleukin (IL)-6, IL-12 and IL-23, and an increase in IL-8 and IL-10 [21]. Second, vitamin D could influence the differentiation and repolarisation of $CD4^+$ T cells through mitigation of the pro-inflammatory signals. In addition, active vitamin D may reduce the inflammatory process by enhancing the population of helper T (Th) type 2 cells and the secretion of IL-4 and IL-10. Similarly, active vitamin D could inhibit the process of inflammation by reducing the population of both tumour necrosis factor-α producing Th1 and IL-17 producing Th17 cells, as well as inflammatory cytokines of interferon-γ and IL-6. Moreover, vitamin D could enhance the population and anti-inflammatory function of regulatory T cells [1, 2]. Concerning B cells, vitamin D could delay the differentiation of B cells into plasma cells and decrease antibody production [22]. In summary, it can be presumed that vitamin D plays a crucial role in the pathophysiology of AAV.

In the correlation analysis, 25(OH)D levels were observed to be considerably related to BVAS and SF-36 PCS and MCS scores, and the correlation coefficients were similar between 25(OH)D and 25(OH)D3. In fact, the absolute levels of 25(OH)D and 25(OH)D3 were very similar; this is consistent with the fact that vitamin D3 is the principal source of vitamin D in the human body [23]. Considering that the level of 25(OH)D in the blood is generally used in the evaluation of vitamin D status [24], the serum level of 25(OH)D was used in the assessment of the association between vitamin D level and disease activity and HRQoL in the patients.

Previous studies have revealed an association between the level of vitamin D and disease activity in several autoimmune rheumatic diseases. A meta-analysis by Lee et al. demonstrated an inverse correlation between the serum level of vitamin D and Disease Activity Score-28 in patients with rheumatoid arthritis [25]. Furthermore, an inverse relationship between circulating 25(OH)D levels and systemic lupus erythematosus disease activity was reported by Guan et al. [6]. Gubatan et al. also revealed low 25(OH)D to be a biomarker for disease activity in patients with inflammatory bowel diseases [26]. In line with these observations, our linear regression revealed an independent association between 25(OH)D level and BVAS in patients with AAV. Conversely, following the performance of linear regression analysis by setting the 25(OH)D levels as a dependent variable, BVAS was exclusively revealed to influence the 25(OH)D level among the included continuous variables, indicating disease activity to be an important factor affecting the level of vitamin D. In contrast to our finding, previous research from Brazil that investigated the association of 25(OH)D with disease activity in patients with GPA showed that 25(OH)D was not associated with the index of BVAS/Wegener's granulomatosis [27]. The discrepant result concerning disease activity that was identified in the observation by Mariana et al. compared to the present study might be associated with the number of patients enrolled, the application of different disease activity measures or the inclusion of patients with GPA only.

Of note, we found that nearly half of healthy controls (48.0%) had vitamin D deficiency, which is in line with other studies that reported high vitamin D deficiency in the general population in South Korea [28, 29]. However, we also found that the proportion of persons with vitamin D deficiency was significantly greater among patients with AAV. In the treatment of AAV, glucocorticoids are widely used for the induction and maintenance of remission in AAV, which could negatively impact bone health [30]. Given that vitamin D plays a critical role in the regulation of bone metabolism, these

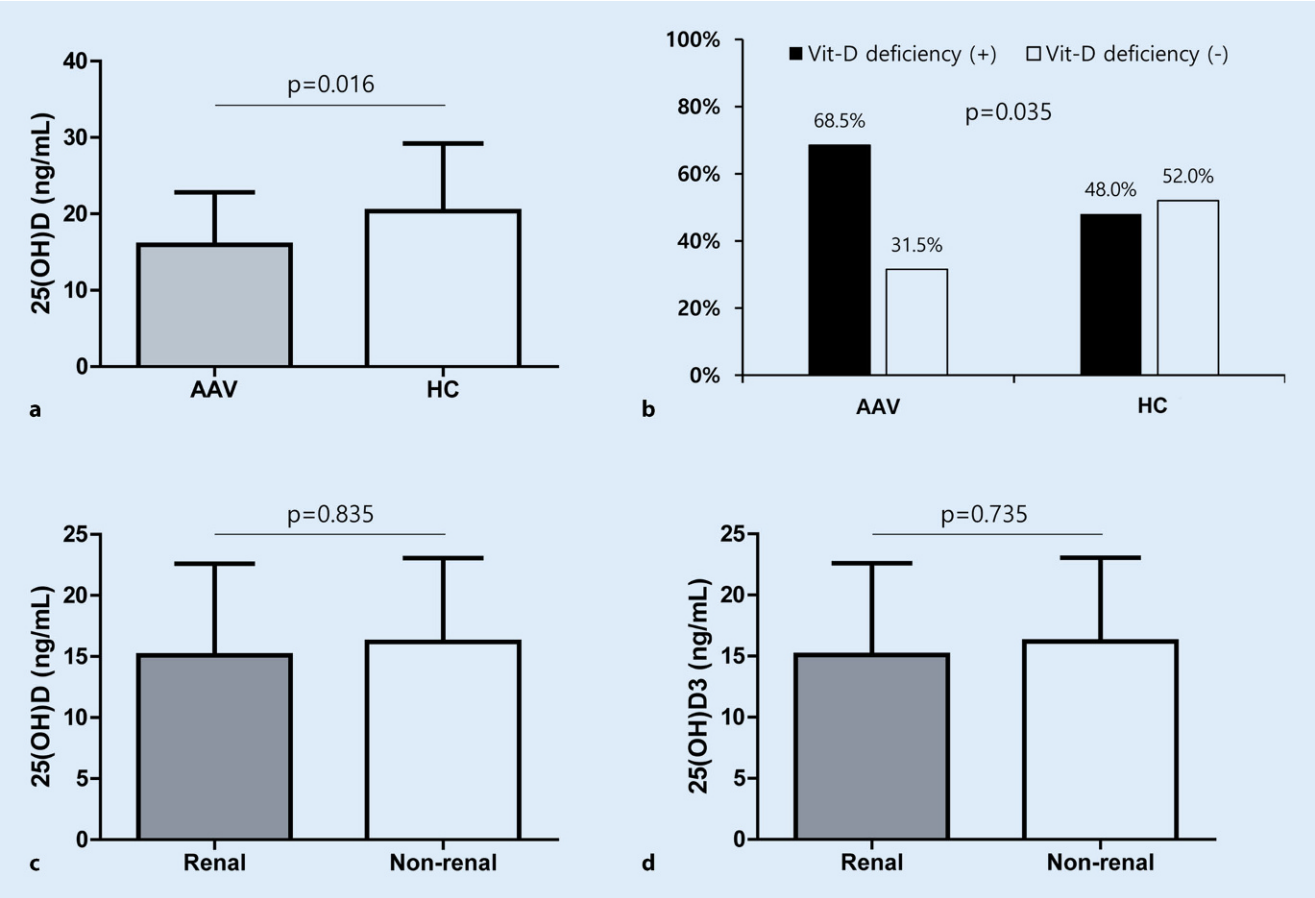

Fig. 1 ▲ Comparison of 25(OH)D between patients with antineutrophil cytoplasmic antibody-associated vasculitis (*AAV*) and controls, and levels of vitamin D in AAV according to the existence of renal involvement. Serum levels of 25(OH)D (**a**) and the proportion of patients with vitamin D deficiency (**b**) were compared between patients with AAV and 50 age- and sex-matched healthy controls. Additionally, serum levels of 25(OH)D (**c**) and 25(OH)D3 (**d**) were compared in patients with AAV based on the presence of renal involvement. Data are shown in median and the error bars indicate interquartile range. *25(OH)D* 25-hydroxy vitamin D, *AAV* antineutrophil cytoplasmic antibody-associated vasculitis, *25(OH)D3* 25-hydroxy vitamin D3, *HC* healthy controls

findings emphasize that supplementation of vitamin D is crucial for maintenance of optimal skeletal health, especially in patients with AAV [31].

There is an existing positive correlation between vitamin D levels and QoL in the general population [32, 33], and there is evidence indicating a relationship between vitamin D levels and QoL in chronic diseases [34]. Consistently, Raczkiewicz et al. revealed a significant correlation between vitamin D levels and SF-36 MCS in patients with rheumatoid arthritis [35]. However, the association between vitamin D levels and QoL in patients with other autoimmune rheumatic diseases remains unclear, particularly in AAV. Surprisingly, in addition to disease activity, our results also showed that the serum level of 25(OH)D was independently related to SF-36 MCS along with CRP levels, which is a representative acute-phase reactant. Nevertheless, as multiple factors, such as smoking, physical activity and nutrition, could equally affect the QoL, the direct relation of QoL to vitamin D level in AAV should be better clarified [36–38].

Seasonal variation is a prevalent factor that could affect the level of vitamin D, and a previous study has demonstrated an existing significant variance in the serum level of 25(OH)D based on the season [39]. Interestingly, the authors observed a closer relationship of serum 25(OH)D with variables of sun exposure, rather than with vitamin D supplementation. Meanwhile, the expression of vitamin D could be similarly affected by the incidence of kidney disease [20]. Concerning patients with AAV, Kemna et al. have established that a decreasing level of vitamin D following an increase in ANCA could indicate disease relapse in patients with renal AAV [11]. However, in this study, differences in serum 25(OH)D and 25(OH)D3 could not be determined based on seasonal variations and the presence of renal involvement. Moreover, no differences were observed in BVAS and SF-36 PCS and MCS scores based on the four seasons. Although it is difficult to precisely explain the reason for the lack of seasonal vitamin D level variation in our patients with AAV, it may be partly attributable to the differences in lifestyle and environmental and geographical factors between South Korea and Europe. Meanwhile, it was previously suggested that seasonal varia-

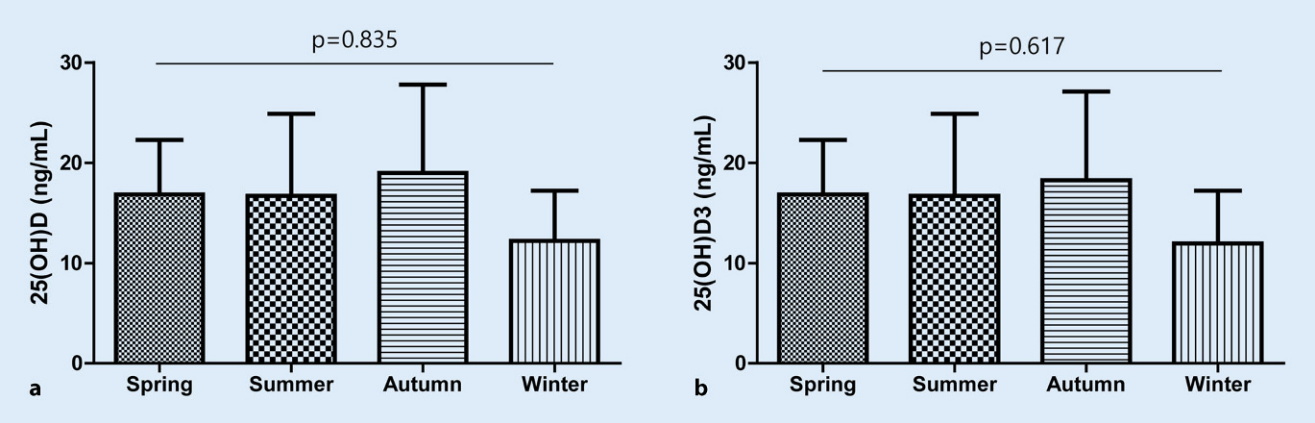

Fig. 2 ▲ Serum levels of 25(OH)D and 25(OH)D3 based on seasonal variations. Serum levels of 25(OH)D (**a**) and 25(OH)D3 (**b**) were compared in patients with AAV based on the meteorological definition of spring, summer, autumn and winter. Data are shown in median and the error bars indicate interquartile range. *25(OH)D* 25-hydroxy vitamin D, *25(OH)D3* 25-hydroxy vitamin D3, *AAV* antineutrophil cytoplasmic antibody-associated vasculitis

tion is present in the general population in South Korea [40, 41]. Even though we hypothesize that it is possible that a disparity may be present in the general population and across different diseases, our data should be verified through further investigations.

To the best of our knowledge, this is the first study establishing an association between vitamin D—serum 25(OH)D and serum 25(OH)D3—and the cross-sectional activity and HRQoL in patients with AAV. However, there were several challenges that could be considered as limitations of this study. First, mechanisms underlying the possible relationship between low serum levels of 25(OH)D and 25(OH)D3 and disease severity and HRQoL of patients with AAV remain unidentified in this study. Second, the study included a relatively small sample size. Third, there was inadequate evidence regarding the possible benefits of vitamin D supplementation for improvement of disease activity and HRQoL in patients with AAV. In addition, data on physical activity or ultraviolet exposure, which possibly influence the level of vitamin D, could not be acquired [42, 43]. Therefore, prospective studies encompassing a larger number of patients with AAV would provide more reliable and validated data.

Conclusion

Patients with AAV exhibited considerably lower serum levels of 25(OH)D than controls, and an independent association was observed between the serum level of 25(OH)D and BVAS and SF-36 MCS scores in patients with AAV. The evaluation of the level of vitamin D could provide clinically helpful information in the management of AAV.

Corresponding address

S.-W. Lee, MD, PhD
Division of Rheumatology, Department of Internal Medicine, Yonsei University College of Medicine
50-1 Yonsei-ro, Seodaemun–gu, 03722 Seoul, Korea (Republic of)
sangwonlee@yuhs.ac

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Compliance with ethical guidelines

Conflict of interest. T. Yoon, S. S. Ahn, J. Y. Pyo, J. J. Song, Y.-B. Park and S.-W. Lee declare that they have no competing interests.

All procedures performed in studies involving human participants or on human tissue were in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards. Approval was granted by the Ethics Committee of Severance Hospital (4-2016-0901). Informed consent was obtained from all individual participants included in the study.

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Availability of data and material. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.