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Original Article

Serum 1,25-dihydroxyvitamin D3 Levels in Patients with Eosinophilic Chronic Rhinosinusitis

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Vitamin D regulates calcium homeostasis and as such affects the production of proinflammatory and anti-inflammatory mediators. We conducted retrospective analyses to investigate the association between serum 1,25-dihydroxyvitamin D3 levels and upper respiratory diseases in Japanese patients with eosinophilic chronic rhinosinusitis (n = 34), non-eosinophilic chronic rhinosinusitis with nasal polyps (n = 11), chronic rhinosinusitis without nasal polyps (n = 31), and allergic rhinitis (n = 7), plus six control subjects without inflammatory disease. We measured the subjects' serum levels of 1,25-dihydroxyvitamin D3 and immunoglobulin E and total eosinophil counts in the peripheral blood. Compared to the controls, the serum 1,25-dihydroxyvitamin D3 levels were significantly higher in the patients with eosinophilic chronic rhinosinusitis, non-eosinophilic chronic rhinosinusitis with nasal polyps, or chronic rhinosinusitis without nasal polyps. No significant difference was detected between the patients with allergic rhinitis and the controls. In the patients with chronic rhinosinusitis, there was no significant correlation between the serum 1,25-dihydroxyvitamin D3 levels and other clinical parameters. We conclude that the serum 1,25-dihydroxyvitamin D3 levels are elevated in Japanese individuals with chronic rhinosinusitis with nasal polyps, and that vitamin D may be a viable therapeutic target for managing chronic rhinosinusitis.

Key words: 1,25-dihydroxyvitamin D3, chronic rhinosinusitis, inflammation, eosinophil, paranasal sinus

Vitamin D is a fat-soluble nutrient known for its classic role in systemic calcium homeostasis. In addition to its traditional function within the endocrine system, recent studies have revealed relationships between vitamin D and chronic illnesses, including cancer, autoimmune conditions, infections, diabetes mellitus, and a range of cardiovascular diseases [1, 2]. This vitamin has also been implicated in the development of atopic diseases, including allergic rhinitis, asthma, and anaphylaxis [3-5]. A population-based study of vitamin D serum levels in 18,224 adults showed an increased prevalence of allergic rhinitis in the vitamin D-deficient subjects [5]. Reduced vitamin D levels are also associated with impaired lung function, increased airway hyper-responsiveness, and reduced glucocorticoid response in patients with asthma, suggesting that vitamin D supplementation in these patients may improve multiple parameters of asthma severity and treatment response [6].

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Chronic rhinosinusitis (CRS) is divided into two subtypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). As two-thirds of intractable and refractory cases of CRSwNP are characterized by eosinophilic inflammation in nasal polyps, the concept of eosinophilic CRS (ECRS) has been increasingly implemented in medical research [7]. Several studies have reported a possible role of vitamin D levels in patients with CRS [8-12], but the findings regarding the effect of vitamin D on CRS have been inconsistent. To the best of our knowledge, no study has examined serum levels of vitamin D in patients with ECRS. Although there is no universally accepted definition for ECRS, a recent study conducted by the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) that evaluated 1,716 patients with refractory CRS proposed diagnostic criteria for ECRS [13].

We conducted the present study to investigate the association between serum levels of 1,25-dihydroxyvitamin D3, a biologically active form of vitamin D, and inflammatory sinonasal diseases, *i.e.*, ECRS, non-eosinophilic CRSwNP, CRSsNP, and allergic rhinitis.

Subjects and Methods

Patients. We retrospectively analyzed the cases of patients who underwent endoscopic sinus surgery at the Kagawa Rosai Hospital or at Okayama University between July 2015 and September 2016. The exclusion criteria were as follows: (1) the use of oral steroids or immunomodulatory agents within the preceding 30 days; (2) the presence of other immunologic (*e.g.*, rheumatoid arthritis, immunodeficiency, cystic fibrosis, ciliary dyskinesia, malabsorption), renal, gastrointestinal, endocrine, or skeletal disorders; and/or (3) a current pregnancy.

The study was conducted in compliance with the Declaration of Helsinki and its later amendments and was approved by the Institutional Review Boards of Okayama University and Kagawa Rosai Hospital. The requirement for the subjects' informed consent was waived due to the retrospective study design.

Definitions. CRS was defined according to the diagnostic criteria outlined in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 [14]. CRSwNP was classified into eosinophilic and non-eosinophilic subgroups based on the JESREC study criteria [13]. ECRS was defined histologically as an average eosinophil count >70 cells per microscopic field (400× magnification) in three fields of the subepithelial area of the evaluated nasal polyps; eosinophils were counted independently by two of the study authors under light microscopy. CRS disease severity was assessed by computed tomography (CT) using the Lund-Mackay radiologic staging system [15].

Allergic rhinitis was diagnosed based on the previously published Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines [16]. Patients with allergic rhinitis reported one or more typical symptoms of chronic rhinitis (rhinorrhea, nasal obstruction, sneezing, nasal itching) and showed positive results for at least one aeroallergen within the multiple allergen simultaneous test. The patients' asthma status was determined based on their medical history.

Control subjects without inflammatory diseases were also recruited for this study. The control group consisted of six adults with cochlear implants: two subjects with progressive sensorineural hearing loss and four with sudden sensorineural hearing loss. Neither progressive sensorineural hearing loss nor sudden sensorineural hearing loss have been reported to be associated with vitamin D levels. The control subjects did not have abnormal shadows in the paranasal sinuses on CT.

Laboratory tests. Peripheral blood samples were collected preoperatively. Each subject's serum levels of 1,25-dihydroxyvitamin D3 were assessed using the Vitamin D Total Assay (Roche Diagnostics, Basel, Switzerland). Two study authors counted the number of eosinophils. Immunoglobulin E (IgE) levels were measured using the CAP system (Pharmacia-Upjohn, Uppsala, Sweden) in accord with the manufacturer's instructions.

Statistical analyses. All data are expressed as the mean ± standard deviations (SD). We used the χ^2-test to examine intergroup differences with respect to categorical variables, and differences in continuous variables were analyzed using the Mann-Whitney *U*-test (for two groups) or the Kruskal-Wallis test (for three or more groups). Spearman's correlation coefficients were used to test the association between any two variables via rank testing. Statistical significance was set at a two-sided p-value of <0.05. All statistical analyses were conducted using the IBM SPSS Statistics platform for Windows (IBM, Armonk, NY, USA).

Results

A total of 89 study subjects (48 men and 41 women) were enrolled: patients with ECRS (n = 34) (mild, n = 8; moderate, n = 15; severe, n = 11), non-eosinophilic CRSwNP (n = 11), CRSsNP (n = 31), allergic rhinitis (n = 7), plus control subjects (n = 6). The demographic data of these five groups are summarized in Table 1.

Significant differences were identified among the groups in terms of age (years), percentage of peripheral blood eosinophils, total IgE levels in the peripheral blood (IU/mL), preoperative CT score, JESREC score, and the coexistence of asthma (%) ($p < 0.05$). No significant difference was detected in the male/female ratio (Table 1). The patients in the ECRS group had significantly higher peripheral blood eosinophil counts, IgE levels, CT scores, JESREC scores, and asthma comorbidity rates compared to the other groups.

Because seasonal inter-and intraindividual variations in serum vitamin D levels have been reported [17], we also analyzed and compared the groups based on the blood examination date of each subject (Table 2). We found no percentage significant differences among the groups in terms of the examination date ($p = 0.37$).

Smoking is considered one of the predominant factors influencing serum levels of vitamin D [8]. There were no significant differences in the percentages of the different smoking statuses between any of the patient groups and the control subjects ($p = 0.12$) (Table 3).

The mean serum 1,25-dihydroxyvitamin D3 levels were 70.08 ± 25.7 pg/mL in the ECRS patients, 70.8 ± 23.7 pg/mL in the non-eosinophilic CRSwNP patients, 63.78 ± 20.6 pg/mL in the CRSsNP patients, 52.38 ± 21.1 pg/mL in the allergic rhinitis patients, and 42.58 ± 11.6 pg/mL in the controls (Fig. 1). The patients with ECRS, non-eosinophilic CRSwNP, and CRSsNP had significantly higher serum levels of 1,25-dihydroxyvitamin D3 compared to the control subjects ($p = 0.005$; $p = 0.005$; and $p = 0.015$, respectively). There was no significant difference in serum 1,25-dihydroxyvitamin D3 levels between the patients with allergic rhinitis and control subjects. The serum

Table 2 Examination dates of the chronic rhinosinusitis patients, allergic rhinitis patients, and control subjects

	ECRS	NECRS	CRSsNP	AR	Control
January (n)	2	1	1	1	1
February (n)	2	1	1	2	1
March (n)	1	2	5	0	0
April (n)	2	0	3	0	0
May (n)	1	3	1	1	0
June (n)	8	0	4	0	2
July (n)	3	1	2	0	1
August (n)	2	1	4	2	0
September (n)	3	1	0	0	0
October (n)	3	0	4	0	0
November (n)	5	1	2	1	1
December (n)	2	0	4	0	0

AR, allergic rhinitis; CRSsNP, chronic rhinosinusitis without nasal polyps; ECRS, eosinophilic chronic rhinosinusitis with nasal polyps; NECRS, non-eosinophilic chronic rhinosinusitis with nasal polyps.

Table 1 Medical and demographic characteristics of the chronic rhinosinusitis patients, allergic rhinitis patients, and control subjects

	ECRS	NECRS	CRSsNP	AR	Control	*P*-value
Number of subjects (n)	34	11	31	7	6	
Male : female ratio	24 : 10	8 : 3	9 : 22	4 : 3	3 : 3	0.215 #
Age (years)	55.6 ± 13.4	49.9 ± 19.0	60.4 ± 15.0	37.1 ± 17.7	38.0 ± 12.5	0.003 *
Peripheral blood eosinophils (%)	8.51 ± 4.90	2.4 ± 1.69	2.70 ± 1.93	4.2 ± 3.73	2.42 ± 0.89	< 0.001 *
IgE (IU/mL)	333 ± 436	362 ± 644	211 ± 693	425 ± 659	−	0.001 *
Pre-operative CT score **	14.5 ± 4.30	10.7 ± 4.78	5.48 ± 3.04	−	0	< 0.001 *
JESREC score	14.6 ± 2.19	8.64 ± 2.01	−	−	−	< 0.001 †
Asthma (%)	41.2	9.1	3.2	0	0	0.025 #

#, Chi-square for independence test; *, Kruskal-Wallis test; †, Mann-Whitney's *U*-test
** Lund-Mackay pre-operative CT score
Values are presented as means ± standard deviations unless otherwise indicated.
AR, allergic rhinitis; CT, computed tomography; CRSsNP, chronic rhinosinusitis without nasal polyps; ECRS, eosinophilic chronic rhinosinusitis with nasal polyps; IgE, immunoglobulin E; JESREC score, the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis score; NECRS, non-eosinophilic chronic rhinosinusitis with nasal polyps.

Table 3 Smoking status and the Brinkman index in the chronic rhinosinusitis patients, allergic rhinitis patients, and control subjects

	ECRS	NECRS	CRSsNP	AR	Control
Smoking status					
No-smoker (n)	14	4	22	3	3
Ex-smoker (n)	16	2	7	1	1
Current smoker (n)	4	5	2	3	2
Brinkman index					
Ex-smoker	453 ± 253	800 ± 481	659 ± 594	240	25
Current smoker	580 ± 177	391 ± 281	320 ± 113	190 ± 252	48 ± 38

AR, allergic rhinitis; CRSsNP, chronic rhinosinusitis without nasal polyps; ECRS, eosinophilic chronic rhinosinusitis with nasal polyps; NECRS, non-eosinophilic chronic rhinosinusitis with nasal polyps.

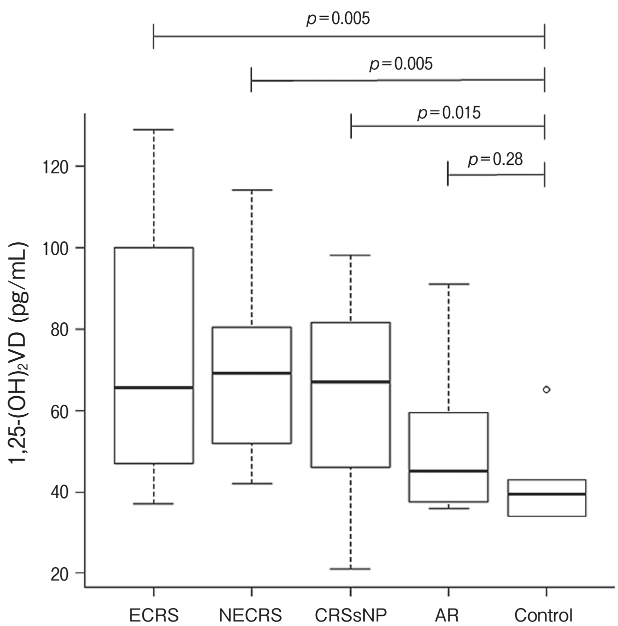

Fig. 1 Serum levels of 1,25-dihydroxy vitamin D3 in the eosinophilic chronic rhinosinusitis (ECRS) patients, non-eosinophilic chronic rhinosinusitis with nasal polyps (NECRS) patients, chronic rhinosinusitis without nasal polyps (CRSsNP) patients, allergic rhinitis patients, and control subjects. *Rectangle*: the range from the 25th to the 75th percentiles. *Horizontal line*: the median. *Vertical line*: the range from the 10th to the 90th percentiles. *Black square*: the mean value. 1,25-$(OH)_2$VD: 1:25-dihydroxyvitamin D3, AR: allergic rhinitis, CRSsNP: chronic rhinosinusitis without nasal polyps, ECRS: eosinophilic chronic rhinosinusitis with nasal polyps, NECRS: non-eosinophilic chronic rhinosinusitis with nasal polyps.

1,25-dihydroxyvitamin D3 levels were significantly higher in the patients without asthma as a potential source of confounding bias; specifically, 20 patients with ECRS ($p = 0.008$) and 10 patients with non-eosinophilic CRSwNP ($p = 0.005$), compared to the levels in the control subjects.

No significant correlations were detected between the serum 1,25-dihydroxyvitamin D3 levels and any of the clinical parameters in the patients with ECRS (preoperative CT score, $r = -0.012$, $p = 0.945$; peripheral blood eosinophil count, $r = -0.150$, $p = 0.383$; IgE level, $r = 0.187$, $p = 0.293$; disease severity, $r = 0.015$, $p = 0.749$; averaged eosinophil count per microscopic field in three fields of the subepithelial area of the evaluated nasal polyps, $r = -162$, $p = 0.401$); or in the patients with non-eosinophilic CRSwNP (preoperative CT score, $r = -0.020$, $p = 0.852$; peripheral blood eosinophil count, $r = 0.311$, $p = 0.340$; IgE level, $r = -0.545$, $p = 0.081$); or in the patients with CRSsNP (preoperative CT score, $r = 0.049$, $p = 0.819$; peripheral blood eosinophil count, $r = 0.008$, $p = 0.976$; IgE level, $r = -0.073$, $p = 0.696$).

Discussion

The results of our analyses demonstrated that the serum 1,25-dihydroxyvitamin D3 levels in patients with CRSwNP were significantly higher than those in control subjects. However, we found no significant correlations between serum 1,25-dihydroxyvitamin D3 levels and clinical parameters in the patients with CRS.

Cholecalciferol, a form of vitamin D3 commonly found in food and oral supplements, is converted to 25-hydroxyvitamin D3, also known as calcidiol, by 25-hydroxylase (encoded by *CYP2R1*). This is the major circulating reservoir of vitamin D3 and is frequently used to determine an individual's vitamin D3 sufficiency status, primarily due to its longer half-life of approx. 15 days. The final step in vitamin D3 activation is the conversion of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3, also known as calcitriol, by 1α-hydroxylase (encoded by *CYP27B1*). This is the biologically active form of vitamin D3 that binds to the vitamin D receptor.

The vitamin D receptor is expressed on nearly all cells in the body and regulates a broad range of functions, including the production of proinflammatory and anti-inflammatory mediators via calcium regulation [18-20]. The catabolism of 1,25-dihydroxyvitamin D3 is controlled by 24-hydroxylase (encoded by *CYP24A1*) [18]. The half-life of circulating 1,25-dihydroxyvitamin D3 is relatively short (approx. 15 h) compared to that of 25-hydroxy vitamin D3 (approx. 15 days) [21].

Upper and lower airway diseases (*e.g.*, asthma, allergic rhinitis, CRS) present with similar clinical and biological features. In addition to asthma and allergic rhinitis, a possible role of vitamin D3 in CRSwNP has been reported. Patients with CRSwNP have been shown to have low vitamin D3 levels independent of age, sex, and asthma status. The vitamin D3 deficiency in these patients has also been found to be correlated with higher-grade objective disease severity, bone erosion, and dendritic cell infiltration. However, the reported findings have been inconsistent, and thus the role of vitamin D3 in patients with CRS remains debatable [8-12, 18].

Various findings at the local or systemic levels with regard to vitamin D3 concentrations in patients with CRS have been described. Wang *et al.* reported that serum 25-hydroxyvitamin D3 levels were lower in patients with CRSwNP and that lower 25-hydroxyvitamin D3 levels were correlated with disease severity in Taiwanese patients [12]. Schlosser *et al.* identified no significant differences in the level of circulating 1,25-dihydroxyvitamin D3 among any of the evaluated study groups (patients with CRSsNP, CRSwNP, and allergic fungal rhinosinusitis as well as control subjects) [18]; they also reported reduced levels of sinonasal 1α-hydroxylase (encoded by *CYP27B1*) and 1,25-dihydroxyvitamin D3. They concluded that the low level of 1,25-dihydroxyvitamin D3 detected in sinonasal tissue in their investigation was not the result of low circulating vitamin D3 levels, and that this finding might instead be caused by low levels of local 1α-hydroxylase activity [18].

Our present findings demonstrated that the serum level of 1,25-dihydroxyvitamin D3 in both patients with eosinophilic CRSwNP and those with non-eosinophilic CRSwNP was higher than that in healthy control subjects. We suspect that the differences in reported findings across studies may be due to interindividual differences in vitamin D metabolism.

The effect of race on vitamin D metabolism has been reported in several investigations. For example, African-American women were found to be at a higher risk of vitamin D deficiency than Caucasian women [22]. Pinto *et al.* reported that Caucasian female control subjects had higher serum 25-hydroxyvitamin D3 levels than African-American female control subjects, and a similar trend was observed in comparative evaluations of Caucasian and African-American males [1]. To the best of our knowledge, there have been no reports on variations in vitamin D metabolism, including enzyme activity in sinonasal tissue, in Japanese subjects.

Other factors may affect 25-hydroxyvitamin D3 levels, including age, daylight exposure, winter season, and disability [23]. Seasonal differences in serum vitamin D3 levels within the same individual (*i.e.*, intraindividual differences) have been described [17]. In the present study, serum vitamin D3 measurements were performed throughout the year, and no seasonal bias was found among the evaluated groups.

Exposure to cigarette smoke has been associated with reduced 25-hydroxyvitamin D3 levels in patients with CRS, as has an impaired ability to convert 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 within human sinonasal epithelial cells [8]. However, most of the previous studies did not focus on the smoking status of their subjects. In the present study, we examined the subjects' smoking status and collected unbiased samples.

Administering vitamin D3 could potentially increase the therapeutic response to glucocorticoids in patients with steroid-resistant asthma [24]. In individuals with CRS, it remains to be determined whether vitamin D3 levels increase as a result of sinus inflammation and/or whether vitamin D3 is involved in the mechanism of sinus inflammation. If the latter is confirmed, the modulation of vitamin D levels may be a novel option for the treatment of intractable CRS.

Our study has several limitations, including a small sample size, differences in age among the groups, and a lack of data regarding the direct sunlight exposure of each subject. Additional studies evaluating the role of metabolic enzymes and intermediates, including 25-hydroxyvitamin D3, are necessary in order to elucidate these effects in Japanese patients with CRS.

In conclusion, our results demonstrated that in a Japanese population, the serum 1,25-dihydroxyvitamin D3 levels in patients with CRSwNP were higher than those in healthy subjects. We thus conclude that vitamin D may be a new therapeutic target for the management of intractable CRS. Our findings could guide future research directions and directly inform medical guidelines.

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