

Evaluation of vitamin D levels in allergic fungal sinusitis, chronic rhinosinusitis, and chronic rhinosinusitis with polyposis

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Background: Vitamin D₃ (VD₃) levels have been recently found to be responsible for a number of immunological, anti-inflammatory and anti-infectious roles. Some studies reported that some forms of allergic fungal rhinosinusitis (AFRS), occurs more commonly in patients who are more susceptible to VD₃ deficiency. The aim of this work was to measure VD₃ levels in patients with AFRS and chronic rhinosinusitis (CRS).

Methods: We report a prospective case control study conducted at Ain Shams University. It included 74 participants divided into 4 groups: group A, 25 patients with AFRS; group B, 15 patients with CRS with nasal polyps (CRSwNP); group C: 15 patients with CRS without nasal polyps (CRSsNP); and group D, 19 controls.

Results: There was a statistically significant ($p < 0.001$) difference of VD₃ between groups A and B compared with groups C and D. There were no statistically significant differences between the 4 groups regard calcium levels. Finally, there was a statistically significant difference in

phosphate levels when we compared groups A and B with groups C and D ($p = 0.001$).

Conclusion: Serum level of VD₃ in patient with CRSwNP and AFRS is significantly lower than that of patients with CRSsNP and control subjects. Although these results do not imply a specific etiological or therapeutic relationship, VD₃ levels may constitute an inexpensive prophylactic and cost-effective option in the therapeutic armamentarium in the control of AFRS and CRSwNP, either by itself or as a synergistic agent with traditional agents. © 2015 ARS-AAOA, LLC.

Key Words:

Chronic sinusitis; Vitamin D; Allergic fungal sinusitis; sinusitis with polypi; allergic rhinitis

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Vitamin D₃ (VD₃) status is traditionally linked with rickets in children and osteomalacia in adults.¹ However, recent studies have highlighted the potential impact of impaired VD₃ status with respect to so-called “nonclassical” effects of VD₃. These include cardiovascular actions,² as an antineoplastic agent,^{3–6} in prevention and/or treatment of infections,⁷ and in association with the immune system.^{8,9} VD₃ has a major impact on the immune system, by di-

rectly affecting monocytes, macrophages, dendritic cells, and T cells.^{10–13} It is a major fighter of inflammation, plays a critical role in prevention and treatment of asthma, and plays a major role in cases of chronic sinusitis and sinus infection.^{10,14} VD₃ also favorably regulates cathelicidin, which is the only antimicrobial agent of its type produced by humans in the skin, in respiratory passages, and throughout the digestive system.^{7,11,12} Previous studies have reported that some forms of allergic fungal rhinosinusitis (AFRS) occur more commonly in patients who are more susceptible to VD₃ deficiency; providing more evidence to support a role of VD₃ as a key player in the immunopathology of chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) and AFRS.¹³ Vitamin D insufficiency is a prevalent health problem all over the world,¹⁰ and this may partly explain the rising incidence of AFRS and other sinus problems.

The aim of this work is to evaluate the possible association between vitamin D levels and AFRS and CRS.

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Subjects and methods

We report a prospective case-control study conducted at Ain Shams University hospitals between March 2013 to July 2014. Written informed consent was obtained from all participants with Institutional Review Board approval. The study included 74 individuals.

Participants were divided into 4 groups:

Group A 25 patients with AFRS diagnosed by the following criteria, nasal polyposis; eosinophilic mucin; computed tomography (CT) scan findings consistent with CRS; histological presence of fungal hyphae or positive fungal culture; and Type I hypersensitivity (atopy) diagnosed by positive skin test or serology;

Group B 15 patients with CRSwNP;

Group C 15 patients with CRS without nasal polyps (CRSsNP). Both diagnosed by CT and endoscopic examination plus postoperative histopathological examination of the polyps for group B and inflamed sinus mucosa only for group C.

Group D control group consisting of 19 healthy volunteers individuals with no history of sinusitis and no endoscopic evidence of inflammatory sinus disease at the time of study.

Patients who had received any form of immunotherapy, steroids, or vitamin supplements within 30 days of surgery were excluded from the study.

The following data was collected:

1. Detailed history taking; ear, nose, and throat (ENT) examination plus through endonasal sinoscopic examination.
2. Radiologic (except for controls): CT paranasal sinuses and plain chest X-ray.
3. Laboratory investigations: complete blood count (CBC) including blood eosinophils, renal, liver function, and blood sugar.
4. All tissue samples obtained during surgery were collected and sent for histopathological examinations.
5. Mycological workup included:
 - Direct film examination for detection of the septate form of fungal infection.
 - Silver stain (Gomori methenamine-silver).
 - Cultures were done on nutrient agar and Sabouraud agar.
6. Measurement of serum level of vitamin D by enzyme-linked immunosorbent assay (ELISA) using an ELISA kit for Human Vit D Immunoassay (Calbiotech, Inc., Spring Valley, CA). All measurements were conducted in the same laboratory, by the same researcher, with the same kit. The blood samples were centrifuged for 15 minutes at 1250g. Subsequently, sera were aliquotted and frozen at -70°C until the day of assay. Serum levels of 25(OH) vitamin D (VD_3) were measured by using a VD_3 enzyme immune assay kit (Catalog No: VD220B; Calbiotech). Based on the principle of solid phase

competitive enzyme-linked immunoassay. The test results are reported in nanomoles per liter (nmol/L). A BioRad PW40 well washer (BioRad, Hercules, CA) was used as the microplate washer in the ELISA assessment of serum levels of VD_3 . An Awareness Technology Stat Fax 2100 (Westport, UK) was used as the ELISA reader.

7. Serum calcium (Ca) and phosphate (PO_4) parameters were measured on a Synchron CX-9 autoanalyzer (Beckman Instruments Inc., Fullerton, CA).

Statistical methods

Data were analyzed using IBM SPSS Statistics version 21 (IBM Corp., Armonk, NY) and MedCalc version 12.5 (MedCalc Software bvba, Ostend, Belgium). The D'Agostino-Pearson test was used to examine the normality of numerical data distribution. Normally distributed numerical variables are presented as mean $\pm$ standard deviation (SD); intergroup differences were compared using 1-way analysis of variance (ANOVA) with application of the Scheffe test for post hoc comparisons whenever ANOVA revealed a statistically significant difference. The Kruskal-Wallis test was used to compare non-normally distributed numerical variables and the Conover test was used for post hoc comparisons. The Pearson chi-square test, or Fisher's exact test when appropriate, was used to compare nominal data. Ordinal data were compared using linear-by-linear association. Multinomial logistic regression was used to examine the relation between VD_3 , Ca level, and PO_4 level, and the type of chronic sinusitis, adjusting for the effect of possible confounders. All tests were 2-tailed. Values of $p < 0.05$ were considered statistically significant.

Results

The study included 74 participants (37 males and 37 females), aged 22 to 48 years (median, 34 years). They were categorized into 4 groups (Table 1).

VD_3 level

The VD_3 levels (in nmol/L) in the different groups were as follows: group A, 32 (23.18 to 43.65); group B, 32.5 (19.38 to 57.33); group C, 125 (63.55 to 223.25); and group D, 129 (56.05 to 177.50).

There was a statistically significant ($p < 0.001$) difference in VD_3 between groups A and B when compared with groups C and D. On the other hand there was no statistically significant difference between group A when compared with group B or between group C when compared with group D.

Serum Ca

The serum Ca levels (in mmol/L) in the 4 studied groups were as follows: group A, 2.46 ± 0.44 ; group B, 2.73 ± 0.29 ; group C, 2.39 ± 0.31 ; and group D, 2.66 ± 0.31 . There were no statistically significant differences between the 4 groups by the Scheffe post hoc test ($p = 0.022$).

TABLE 1. Patient characteristics in the 4 study groups*

Variable	AFRS (n = 25)	CRSwNP (n = 15)	CRSsNP (n = 15)	Control (n = 19)	p
Age (years)	33.3 ± 14.6	30.7 ± 16.4	41.5 ± 13.8	32.8 ± 13.7	0.188 ^a
Male/female (n)	10/15	9/6	8/7	10/9	0.633 ^b

*Values are presented as mean ± SD or ratio.

^aOne-way ANOVA.

^bPearson chi-square test.

AFRS = allergic fungal rhinosinusitis; ANOVA = analysis of variance; CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; SD = standard deviation.

TABLE 2. Quantitative assay of serum VD₃, calcium, and phosphate levels in the 4 study groups*

Variable	AFRS (n = 25)	CRSwNP (n = 15)	CRSsNP (n = 15)	Control (n = 19)	p
Vitamin D ₃ level (nmol/L)	32 (23.18–43.65) ^a	32.5 (19.38–57.33) ^a	125 (63.55–223.25)	129 (56.05–177.50)	<0.001 ^b
Calcium level (mmol/L)	2.46 ± 0.44	2.73 ± 0.29	2.39 ± 0.31	2.66 ± 0.31	0.022 ^{c,d}
Phosphate level (mmol/L)	1.17 ± 0.44 ^e	1.06 ± 0.27 ^e	1.24 ± 0.27	1.60 ± 0.46	0.001 ^c

*Values are median (interquartile range) or mean ± SD.

^aAdjusted value of p < 0.05 vs CRS and control (Conover test).

^bKruskal-Wallis test.

^cOne-way ANOVA.

^dNo statistically significant differences by the Scheffe post hoc test.

^eAdjusted value of p < 0.05 vs CRS and control (Scheffe test).

AFRS = allergic fungal rhinosinusitis; ANOVA = analysis of variance; CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; SD = standard deviation; VD₃ = vitamin D₃.

TABLE 3. Detailed qualitative assay of serum VD₃, calcium, and phosphate levels in the 4 study groups

Variable	AFRS (n = 25)	CRSwNP (n = 15)	CRSsNP (n = 15)	Control (n = 19)	p
VD ₃ level					
Optimal	2 (8.0)	2 (13.3)	9 (60.0)	13 (68.4)	<0.001 ^a
Sufficient	1 (4.0)	3 (20.0)	3 (20.0)	1 (5.3)	
Hypovitaminosis	4 (16.0)	2 (13.3)	1 (6.7)	3 (15.8)	
Vitamin D deficiency	18 (72.0)	8 (53.3)	2 (13.3)	2 (10.5)	
Calcium level					
Normal	17 (68.0)	15 (100.0)	12 (80.0)	18 (94.7)	0.020 ^b
Hypocalcemia	8 (32.0)	0 (0.0)	3 (20.0)	1 (5.3)	
Phosphate level					
Normal	20 (80.0)	15 (100.0)	15 (100.0)	18 (94.7)	0.071 ^b
Hypophosphatemia	5 (20.0)	0 (0.0)	0 (0.0)	1 (5.3)	

Values are n (%).

^aLinear-by-linear association.

^bFisher's exact test.

AFRS = allergic fungal rhinosinusitis; CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; VD₃ = vitamin D₃.

Serum PO₄

The mean serum PO₄ levels (in mmol/L) in the 4 groups were as follows: group A, 1.17 ± 0.44; group B, 1.06 ± 0.27; group C, 1.24 ± 0.27; and group D, 1.60 ± 0.46. There was a statistically significant difference when we compared groups A and B with groups C and D (p = 0.001).

The quantitative assay of serum VD₃, Ca, and PO₄ levels in the 4 study groups is shown in Tables 2 and 3.

Multinomial logistic regression was used to examine the relation between VD₃, Ca, and PO₄ levels and the type of disease, adjusting for the effect of possible confounders (Table 4). The test confirmed the results obtained by the other statistical tests.

TABLE 4. Results of multinomial logistic regression for determinants of the type of sinusitis*

Form of sinusitis	b	SE	Wald	df	p	Exp(B)	95% CI for Exp(b)		
							Lower bound	Upper bound	
AFRS									
Intercept	5.29	3.33	2.519	1	0.112				
Age (years)	0.03	0.03	1.189	1	0.275	1.03	0.98	1.09	
Male gender	−0.64	0.82	0.612	1	0.434	0.52	0.10	2.64	
VD ₃ level (nmol/L)	−0.05	0.02	10.621	1	0.001	0.95	0.92	0.98	
Calcium level (nmol/L)	−2.30	1.39	2.756	1	0.097	0.10	0.01	1.52	
Phosphate level (nmol/L)	2.85	1.48	3.703	1	0.054	17.22	0.95	312.78	
CRSwnP									
Intercept	−4.06	4.26	0.907	1	0.341				
Age (years)	−0.02	0.03	0.254	1	0.614	0.98	0.92	1.05	
Male gender	0.40	0.92	0.186	1	0.666	1.49	0.24	9.08	
VD ₃ level (nmol/L)	−0.03	0.01	6.586	1	0.010	0.97	0.94	0.99	
Calcium level (nmol/L)	0.12	1.70	0.005	1	0.944	1.13	0.04	31.41	
Phosphate level (nmol/L)	5.00	1.61	9.682	1	0.002	148.75	6.37	3473.91	
CRSsNP									
Intercept	5.33	3.25	2.677	1	0.102				
Age (years)	0.08	0.04	4.545	1	0.033	1.08	1.01	1.16	
Male gender	0.11	0.83	0.019	1	0.890	1.12	0.22	5.70	
VD ₃ level (nmol/L)	0.00	0.01	0.172	1	0.678	1.00	0.99	1.01	
Calcium level (nmol/L)	−4.63	1.62	8.136	1	0.004	0.01	0.00	0.23	
Phosphate level (nmol/L)	2.59	1.47	3.110	1	0.078	13.28	0.75	235.38	

*The reference category is: Control.

AFRS = allergic fungal rhinosinusitis; b = regression coefficient; CI = confidence interval; CRS = chronic rhinosinusitis; CRSsNP = CRS without nasal polyps; CRSwNP = CRS with nasal polyps; df = degrees of freedom; Exp(b) = proportional hazard; SE = standard error; VD₃ = vitamin D₃; Wald = Wald chi square statistic.

Discussion

Although the definite cause of the persistent symptomatic inflammation associated with CRS is unknown, it is thought to be the result of numerous interactions between environmental factors and the host immune system.^{11,15} Today there is increasing evidence suggests that VD₃ plays an important role in respiratory health.¹⁶ Increased VD₃ levels were associated with reduced likelihood for being hospitalized and reduced use of anti-inflammatory medications in asthmatic patients.¹⁶ VD₃ levels are inversely associated with the occurrence of upper respiratory tract infections, and this association was even stronger in those with asthma.¹⁰ In the upper airway, many reports have examined the role of VD₃ in allergic rhinitis. Wjst and Hypponen¹⁷ found that the prevalence of allergic rhinitis increased across quartile groups of low VD₃ serum levels. Pinto et al.¹⁸ observed that patients with allergic rhinitis have lower VD₃ levels than race- and age-matched

controls, suggesting that VD₃ has a potential role in upper respiratory disease.

This prospective study showed that serum level of VD₃ in patient with CRSwNP and AFRS is significantly lower ($p < 0.001$) than that of patients with CRSsNP and control subjects (Fig. 1). In accordance with Mulligan et al.,¹³ they stated that both CRSwNP and AFRS patients were identified as being VD₃-insufficient compared to control and CRSsNP. There is increasing evidence to support a role for VD₃ as a key player in the immunopathology of CRSwNP and AFRS. Moreover, VD₃ deficiency may be associated with increased bone erosion in CRSwNP and AFRS.^{13,19,20} Also these studies support a role for VD₃ as a key player in the immunopathology of CRSwNP.²⁰⁻²⁴ McCarty et al.²⁵ reported that low VD₃ levels were documented in patients with chronic CRSwNP, and VD₃ was shown to inhibit proliferation of nasal-polyp fibroblasts that may confirm its anti-inflammatory effect.

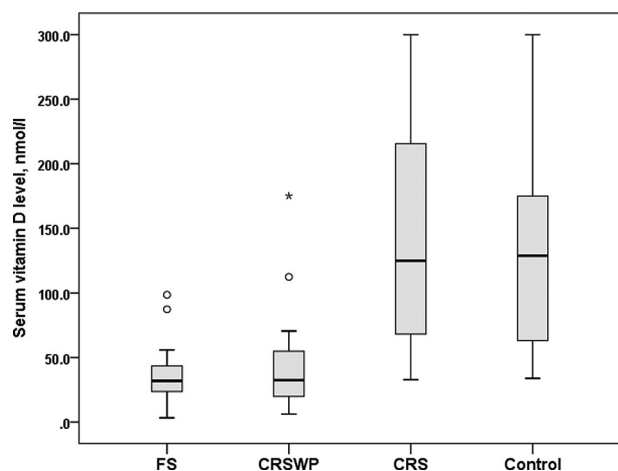


FIGURE 1. Box plot showing serum vitamin D level in the 4 study groups. CRS = chronic rhinosinusitis without nasal polyps; CRSWP = chronic rhinosinusitis with nasal polyps; FS = fungal sinusitis.

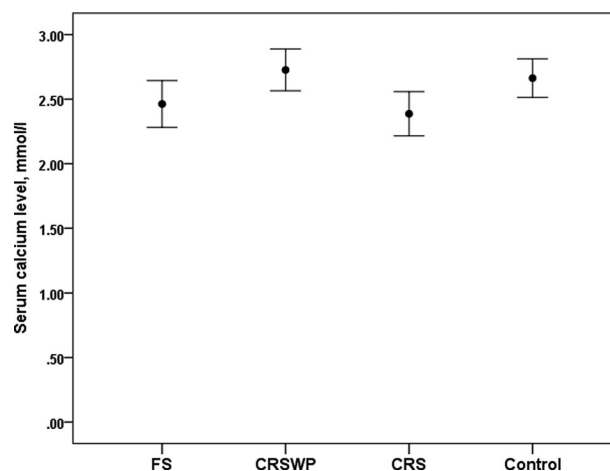


FIGURE 2. Mean serum calcium level in the 4 study groups. Error bars represent 95% CI. CI = confidence interval; CRS = chronic rhinosinusitis without nasal polyps; CRSWP = chronic rhinosinusitis with nasal polyps; FS = fungal sinusitis.

Another study suggests the effectiveness of VD₃ when used by high therapeutic dose, in reducing the size of nasal polyps, and its ability to restore the nasal mucosa near its normal state. These findings raise possibilities for the development of more efficient and specific types of therapy in nasal polyposis, especially in patients unfit for surgery or who refuse surgery and in recurrent cases.^{26,27} The importance of the cellular effects of VD₃ within the lung for host response against inflammation and treatment of allergic lung disease such as asthma has strong evidence to support it. Epidemiological studies suggest that vitamin D deficiency predisposes individuals not only to viral respiratory tract infections but also to mycobacterial infections.¹⁹

On the other hand, in their studies, Apuhan et al.²⁸ could not prove any association between serum VD₃ level and CRSwNP. Also, in the recently published Vitamin D and Asthma (VIDA) study, VD₃ supplementation failed to show an improvement in asthma control in adults.²⁹ Our study showed that VD₃ levels were not influenced by gender or age among the 4 groups studied.

There was no statistically significant differences regarding Ca level between the 4 groups by using the Scheffe post hoc test. Several studies also showed no relation between VD₃ concentrations and Ca absorption in children and adolescents (Fig. 2).^{30–34}

On the other hand, there was a significant decrease in the serum PO₄ level in groups A and B compared with groups C and D (Fig. 3). This can be explained by the following: vitamin D deficiency stimulates the parathyroid glands, leading to secondary hyperparathyroidism, which maintains serum calcium in the normal range at the expense of mobilizing calcium from the bone and increases urinary phosphate loss, resulting in a decrease in serum phosphate level. On the contrary, no relationships were detected between levels of serum ionized calcium, phosphate, and serum vitamin D metabolites in the study conducted by Brot et al.³⁵

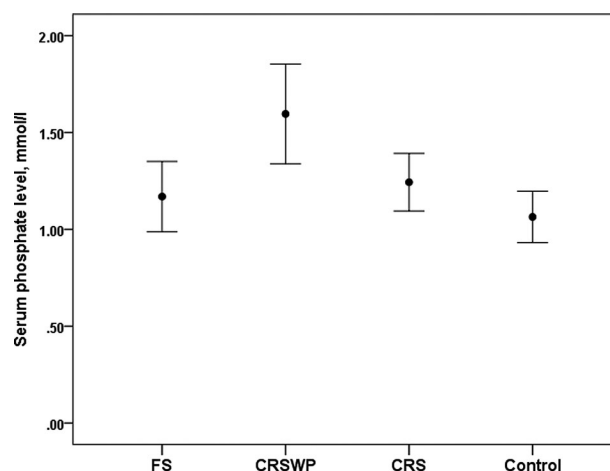


FIGURE 3. Mean serum phosphate level in the 4 study groups. Error bars represent 95% CI. CI = confidence interval; CRS = chronic rhinosinusitis without nasal polyps; CRSWP = chronic rhinosinusitis with nasal polyps; FS = fungal sinusitis.

Conclusion

Serum level of VD₃ in patient with CRSwNP and AFRS is significantly lower than that of patients with CRSsNP and control subjects. VD₃ may constitute an inexpensive prophylactic and cost-effective option in the therapeutic armamentarium in reducing inflammation either by itself or as a synergistic agent to traditional agents. However, because there is no consensus on the serum vitamin D levels to consider appropriate for global health, the doses to use for its supplementation, or the cutoffs for its deficiency, we are in need of large, controlled, prospective studies on VD₃ supplementation to clarify whether it has a role in the pathogenesis, prevention of and treatment for AFRS, CRSwNP, and allergic conditions. 🌐

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