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Vitamin D deficiency are associated with subjective disease severity in Chinese patients with chronic rhinosinusitis with nasal polyps

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ABSTRACT

Objective: To evaluate the serum vitamin D level in patients with chronic rhinosinusitis with nasal polyps and its correlation with the disease severity.
Setting: Hospital of Zhejiang University.
Study design: Retrospective analysis of collected data.
Subjects and methods: Patients with chronic rhinosinusitis with or without nasal polyps who underwent endoscopic sinus surgery were recruited. Demographic information including age, gender, body mass index, smoke history, atopic status and asthma was collected. Disease severity was measured by the Lund-Mackay CT score and Sino-Nasal Outcome Test-22 score. Serum 25-hydroxyvitamin D3 was measured by enzyme-linked immunosorbent assay preoperatively.
Results: Serum 25-hydroxyvitamin D3 levels were significantly lower in patients with nasal polyps (CRSwNP, 38.2 ± 9.1 nmol/L; CRSsNP, 48.94 ± 12.1 nmol/L; control, 54.1 ± 17.1 nmol/L. $p < 0.001$), and the levels were significantly associated with the preoperative Sino-Nasal Outcome Test-22 score ($p = 0.013$), but not with the Lund-Mackay score ($p = 0.126$). Furthermore, serum 25-hydroxyvitamin D3 levels were associated with the subjective improvement six months postoperatively ($p < 0.001$),
Conclusion: Serum 25-hydroxyvitamin D3 levels are lower in Chinese CRSwNP patients. These 25-hydroxyvitamin D3 levels are associated with SNOT-22 score. Preoperative 25-hydroxyvitamin D3 level may impact on the symptom improvement after surgery.

1. Introduction

Chronic rhinosinusitis (CRS) is a sinonasal mucosa inflammatory disease. It has traditionally been classified by phenotype, defined as the presence or absence of polyps. But evidence suggests that chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) are unique disease entities associated with separate and distinct inflammatory milieu [1,2]. Furthermore, CRSwNP in Western is most closely associated with Th2 cytokine skewing; Chinese patients with CRSwNP showed a Th1/Th17 cell pattern instead [3]. These observations indicate immunologic heterogeneity among different regions within the same disease phenotype.

Vitamin D is a potent steroid hormone involved in the regulation of bone mineralization and calcium homeostasis; it is synthesized in the skin and then undergoes hydroxylation to produce biologically active 1α, 25-dihydroxyvitamin D3. The discovery that most tissues and cells have a vitamin D receptor has provided new insights into the function of this vitamin [4]. It is now recognized as a key regulator of the immune system due to the regulation of a variety of cell types, such as dendritic cells, monocytes, macrophages, and T cells [5,6]. Recent studies have evidenced the anti-inflammatory function of vitamin D for CRSwNP. It can reduce the proliferation of nasal polyp fibroblasts and its secretion of matrix metalloproteinases and cytokines [7–13]; it can augment innate immunity through the modulation of cathelicidin production by the sinonasal mucosa [14]. In addition, vitamin D deficiency increases sinus mucosa dendritic cells in pediatric CRSwNP [15], and administration of vitamin D may relieve the symptoms and signs of CRS [16,17].

The body vitamin D status is measured by serum 25-hydroxyvitamin D3 (25VD3) level that is influenced by age, gender, and race [18]. To date, serum 25VD3 has been increasingly considered as an independent predictor of risk for many chronic illnesses [4]. Although several studies assessing CRS have shown an association with lower serum 25VD3 and this has specifically been linked to the presence of nasal polyps, there

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are still conflict results from patients with CRSwNP from different races [19–23]. To our knowledge, few studies have examined the vitamin D status in Chinese patients with CRS. Therefore, we sought to determine whether serum vitamin D levels might be associated with CRS, and to explore its contribution to the disease severity and treatment results.

2. Materials and methods

This study was performed with approval of the Institutional Review Board of the first affiliated hospital of Zhejiang University. A review was performed of prospective collected data of patients with CRS who underwent ESS (endoscopic sinus surgery) at our hospital. Diagnose of CRSwNP ($n = 42$) and CRSsNP ($n = 25$) met the definition in 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) [1]. Patients with nasal septum deviation and free of radiographic and endoscopic evidence of inflammatory sinus disease at the time of surgery were used as control ($n = 21$). Exclusion criteria included use of daily vitamin D supplements, use of oral steroids or immunomodulatory agents within 30 days before admission, other systemic disorders that affect the absorbing and metabolism of vitamin D, and pregnancy. Demographic information was collected, including age, gender, body mass index (BMI) and smoke history. Atopic status was determined by elevated serum specific immunoglobulin E (IgE) level. Asthma status was determined by patient history. Serum calcium and phosphate parameters were collected prior to surgery. The objective disease severity was assessed by Lund-Mackay (LM) CT score. The Sino-Nasal Outcome Test-22 score (SNOT-22) was collected preoperatively and six months postoperatively. Subjective improvement was assessed using SNOT-22 delta score (score on the postoperative six months minus the baseline score). Serum 25VD3 level was measured by enzyme-linked immunosorbent assay (ELISA; Alpco Immunoassays, Salem, New Hampshire) prior to surgery. Insufficient vitamin D level was defined as < 30 ng/mL and deficient level was defined as < 20 ng/mL according to the guideline [24].

2.1. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 23 (IBM Corp, Armonk, NY). Proportions were assessed using chi-square analysis. Parametric data were analyzed using one-way analysis of variance (ANOVA). The Kruskal-Wallis test was used for nonparametric data. Correlations were examined using Pearson's analysis. $P < 0.05$ was considered significant.

3. Results

The study included 88 subjects (46 males and 42 females), aged 18 to 72 years (mean, 43 years). Demographic data were summarized in Table 1. There were no significant differences between three groups regarding age, gender, BMI, smoke history, atopic status and asthma.

Table 1
Patient characteristics in three groups.

	CRSwNP (42)	CRSsNP (25)	Control (21)	*P* value
Age (years)	46.50 ± 14.68	41.56 ± 15.54	39.61 ± 12.67	0.159
Male/female (*n*)	21/21	12/13	13/8	0.591
BMI (mean)	25.43 ± 6.14	23.7715 ± 2.72	23.13 ± 2.84	0.513
Asthma/non-asthma	5/37	3/22	2/21	0.634
Atopy/non-atopy	9/33	7/18	5/16	0.83
Smoke/non-smoke	8/34	6/19	3/18	0.707

CRSwNP = CRS with nasal polyps; CRSsNP = CRS without nasal polyps; BMI = body mass index.

Table 2
Distribution of circulating VD3 status in three groups.

	CRSwNP	CRSsNP	Control	*P* value
VD3 level				
Normal (> 30 ng/mL)	0	0	2 (10%)	
Insufficiency (20–30 ng/mL)	3 (7%)	11(44%)	11(52%)	
Deficiency (≤20 ng/mL)	39 (93%)	14 (56%)	8 (38%)	0.000

VD3 = 25-hydroxyvitamin D3; CRSwNP = CRS with nasal polyps; CRSsNP = CRS without nasal polyps.

Table 3
Serum levels of VD3, calcium, and phosphate in three groups.

	CRSwNP	CRSsNP	Control	*P* value
VD3 level (nmol/L)	38.2 ± 9.1	48.94 ± 12.1	54.1 ± 17.1	0.000
Calcium level (mmol/L)	2.27 ± 0.12	2.29 ± 0.11	2.3 ± 0.09	0.468
Phosphate level (mmol/L)	1.26 ± 0.42	1.14 ± 0.27	0.97 ± 0.19	0.000

VD3 = 25-hydroxyvitamin D3; CRSwNP = CRS with nasal polyps; CRSsNP = CRS without nasal polyps.

3.1. Serum 25VD3 levels

Distribution of serum 25VD3 status in three groups was detailed in Table 2. Serum 25VD3 level in patients with CRSwNP was significantly lower than those in patients with CRSsNP or control (subjects with CRSwNP, 38.2 ± 9.1 nmol/L; subjects with CRSsNP, 48.94 ± 12.1 nmol/L; control subjects, 54.1 ± 17.1 nmol/L. $P < 0.001$). However, the difference of serum VD3 levels between CRSsNP and control group was not significant. (Table 3).

3.2. Serum calcium and phosphate levels

The serum calcium levels (in mmol/L) in the three studied groups were 2.27 ± 0.12 in CRSwNP; 2.29 ± 0.11in CRSsNP; and 2.3 ± 0.09 in the control group respectively. The differences between these three groups were not significant ($P = 0.468$). In contrast, serum phosphate levels (in mmol/L) were found to be higher in the CRSwNP group (1.26 ± 0.42) when compared with CRSsNP (1.14 ± 0.27) and control group (0.97 ± 0.19) ($p < 0.001$). On the other hand, there was no statistically significant difference in serum phosphate levels between CRSsNP and control subjects (Table 3).

3.3. Correlations between serum 25VD3 level and disease severity in CRSwNP group

In patients with CRSwNP, serum 25VD3 level was not significantly associated with LM score ($R = -0.240$, $p = 0.126$) (Fig. 1), but with preoperative SNOT-22 score ($R = -0.378$, $p = 0.013$) (Fig. 2). Furthermore, improvement of SNOT-22 score postoperatively was significantly correlated with 25VD3 level (thirty-four patients had SNOT-22 score available at six months postoperatively) ($R = 0.567$, $p < 0.001$) (Fig. 3).

4. Discussion

The current study evaluated the circulating 25VD3 status in Chinese patients with CRS. Our data showed that the serum 25VD3 level in patients with CRSwNP was significantly lower than those in patients with CRSsNP or the control. The lower 25VD3 level in CRSwNP was inversely correlated with preoperative SNOT-22 score. Moreover, our study proved an influence of 25VD3 level on the symptom improvement after surgery in CRSwNP.

Vitamin D is a potent immunomodulator that has been implicated in the development of respiratory health. Its deficiency is inversely

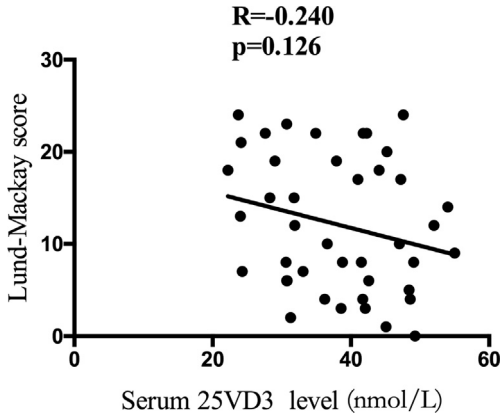

Fig. 1. Relationship between serum VD3 (25-hydroxyvitamin D3) level (x-axis) and Lund-Mackay score (y-axis) in patients with CRSwNP ($R = -0.240$, $p = 0.126$).

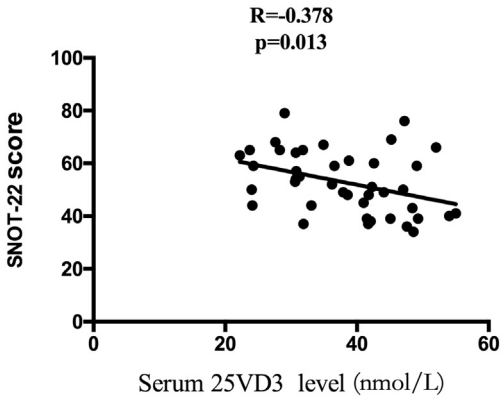

Fig. 2. Relationship between serum VD3 (25-hydroxyvitamin D3) level (x-axis) and SNOT-22 score (y-axis) in patients with CRSwNP ($R = -0.378$, $p = 0.013$).

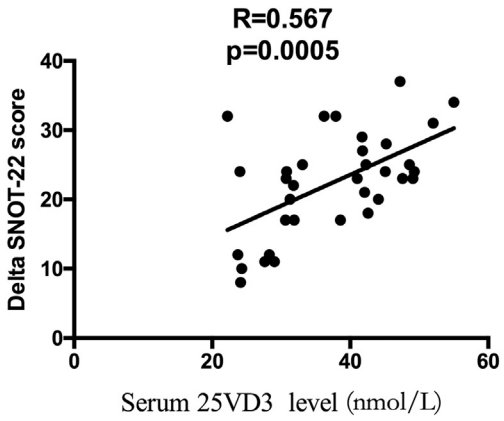

Fig. 3. Relationship between serum VD3 (25-hydroxyvitamin D3) level (x-axis) and the reduction of SNOT-22 scores (delta SNOT-22) (y-axis) in patients with CRSwNP ($R = 0.567$, $p < 0.001$).

correlated with upper respiratory tract infections [25]. Recent evidence supports that vitamin D may play an important role in CRS [7–13]. Furthermore, high therapeutic dose of vitamin D may effectively reduce the nasal polyp size and restore the nasal mucosa near its normal state [17]. Previous studies have reported that 25VD3 deficiency/inefficiency are more common in CRSwNP [19–21,26], and this was confirmed by our data. Our study also revealed lower serum 25VD3 level in CRSwNP cohort than CRSsNP or the control group in Chinese patients. In our study, 25VD3 deficiency was present in 93% of CRSwNP group, 56% of CRSsNP group, and 38% of the control respectively; meanwhile, 25VD3 insufficiency was present in 7% of CRSwNP, 44% of CRSsNP, and 52% of control respectively. In accordance with Wang et al., they also illustrated that patients with CRSwNP were identified as being VD3-insufficient compared to CRSsNP in a study of 45 Taiwanese patients. However, the proportion of VD deficiency was 45.5% in their CRSwNP cohort, which was much lower than that of ours [26]. One possible explanation was that their patients lived in a southern city in Taiwan (lower latitude) with more intense sun exposure than us. Given race is a well-known contributing factor to 25VD3 deficiency [18], in some ways it is not surprising that there are some arguments concerning the systemic 25VD3 status in patients with CRSwNP from different races. Pinto et al. showed significantly lower serum VD3 levels in African Americans with CRS compared with race- and sex-matched controls [20]. This observation was confirmed by Mostafa and Schlosser's reports. They also found significantly lower VD3 levels in African American patients with CRSwNP compared with race-matched control subjects [19,21]. On the contrary, two studies in Turkey showed the circulating levels of 25VD3 were equivalent between patients with CRSwNP and control [22,23]. Together, the above studies along with our investigation highlight the fact that there are still many controversies regarding vitamin D status in CRS. Further carefully controlled epidemiological studies should be performed to clarify the association between the 25VD3 level and CRS.

Given the widespread effects of vitamin D on immune system [5,6], its potential role in mucus overproduction [27], and its antiangiogenic and antiproliferative properties [28], it is rational to hypothesize that vitamin D may have impact on the treatment result after ESS. To our knowledge, however, to date no published study has examined the influence of serum vitamin D on the symptom improvement after ESS. In our study, the improvement of SNOT-22 scoring was found to be positively correlated with 25VD3 level. The result from our study supports that serum vitamin D levels could be added to the routine workup of patients performing ESS and these data could be used to potentially help determine symptom improvement after surgery. Within this study, significant correlation was observed between circulating 25VD3 level and SNOT-22 score in CRSwNP, which was conflicted with Schlosser and Christensen's researches, who stated that the serum 25VD3 level was not associated with SNOT-22 score but with the local genes expression essential in vitamin D metabolism in CRSwNP [29,30]. Meanwhile, the circulating level of 25VD3 was not correlated with LM score in our research, which was in line with the result reported by Wang et al. [26], but not with that of Schlosser's study [21]. It is possible that these discrepancies were due to CRS subgroups or the heterogeneity of CRS from different races being assessed in these studies. With respect to evidence from the published literature, the result presented here stresses the fact that systematic 25VD3, as a parameter for the disease severity of CRS, was to be determined.

In our study, serum calcium levels were equivalent among the three subgroups, whereas the serum phosphate level significantly decreased in CRSwNP cohort. This is likely that vitamin D deficiency decreases intestinal calcium absorption, and consequently results in hyperparathyroidism. The secondary hyperparathyroidism can mobilize calcium from the bone to maintain the serum calcium level, accompanied with phosphaturia, which leads to an increasing of urinary phosphate loss and thus a low-normal or low serum phosphorus level [4]. Our data was in line with Mostafa's report. They also found equal serum calcium levels in their cohort despite the lower concentration of serum VD3 level in patients with CRSwNP, who also had lower serum phosphate levels [19].

There were a number of drawbacks to our study. Firstly, the small sample size may have underpowered the study. Secondly, our study population was not categorized by endotype, which may provide a better comparison subgroup. A larger sample size in future studies may enable analysis to be performed between CRS subgroups assessed by tissue eosinophilia or other cytokine markers.

5. Conclusions

Chinese patients with CRSwNP have reduced circulating 25VD3 levels compared to CRSsNP and control subjects, and the levels of 25VD3 are associated with subjective disease severity. Furthermore, systematic VD3 may be a predictor for symptom improvement after ESS. Further carefully controlled investigation is warranted to elucidate the complex interplay between VD3 and CRS before recommending widespread therapeutic protocols.

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Conflict of interest

The authors declare that they have no conflict of interest.

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None.

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