

The relationship between serum vitamin D and chronic rhinosinusitis: A systematic review

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ABSTRACT

Background: An exciting development in upper respiratory tract disease is the pathophysiology of vitamin D (VD3). There now is substantial literature to indicate that VD3 acts as an immunomodulator of adaptive and innate immunity locally within the respiratory epithelium. Chronic rhinosinusitis (CRS) places a relatively large socioeconomic burden on developed nations, yet remains a difficult disease to treat. VD3, therefore, has become an area of clinical interest because it may provide an adjunctive drug therapy option in CRS, thereby potentially improving the quality of life of these patients.

Objective: A systematic review of the relationship among serum VD3 levels, CRS phenotype, and disease severity by using outcome assessments.

Methods: A systematic search was performed by using the PubMed, MEDLINE, and EMBASE databases. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. Studies that measured serum VD3 levels and correlated the measurements to any subtype of CRS (with or without nasal polyps) were included for qualitative analysis.

Results: Seven articles were included (four prospective and three retrospective studies), with a total of 539 patients. There were significantly lower VD3 levels in the polypoid phenotypes of CRS compared with controls. Low VD3 levels were often associated with an increased degree of inflammation.

Conclusion: The available evidence indicated that there is a significant relationship between low VD3 levels and polypoid CRS phenotypes. The association between VD3 levels and disease severity and VD3 potential for drug therapy remains unclear, which warrants further research in the area.

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Chronic rhinosinusitis (CRS) is a disease of the upper respiratory tract characterized by diffuse inflammation of the sinonasal mucosa.¹ According to recent national epidemiologic data, it is estimated that >1.9 million Australians have the disease.² CRS remains difficult to treat in many cases and represents a large socioeconomic burden.

Recent consensus guidelines define CRS by using sinonasal symptoms combined with radiologic and/or endoscopic findings.¹ The pathophysiology of CRS is still largely unknown, but it has been described as a dysfunctional host-environment interaction.¹ This overall concept is in agreement with the current theories of pathogenesis of CRS, the superantigen,³ and immune barrier hypotheses,⁴ which describe a balance of interactions among the host, commensal flora, potential pathogens, and exogenous stresses.

CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) are thought to be the end product of T-helper 1 (Th1) and Th2 cell skewing, respectively.^{5,6} Recent evidence indicates that CRSsNP and CRSwNP are unique disease entities with distinct histopathologic findings.⁷ To complicate matters further, results of several studies showed that T-cell lineage varies, depending on the individual's comorbid profile and race,^{8,9} which indicates that many factors influence T-cell skewing.

Vitamin D (VD3) has long been recognized for its role in bone mineralization and calcium homeostasis.¹⁰ Recently, there has been a focus on the nonskeletal effects of VD3, including cardiovascular, autoimmune, and immunomodulatory roles.^{11,12} VD3 is initially generated in the skin from nonenzymic conversion of pro-VD3 to pre-VD3. The liver contains 25-hydroxylase, which catalyzes the conversion of pre-VD3 to 25-hydroxy-VD3, the form that most accurately relates to skin and dietary exposure. 25-hydroxy-VD3 finally converted to the active metabolite 1,25-dihydroxy-VD3 by the kidneys, although other tissues, including respiratory epithelial cells, also contain functioning 1- α -hydroxylase.¹³

Active VD3 causes cellular responses by binding to an intracellular VD3 receptor, which acts as a ligand-dependent transcription factor that affects the expression of various genes. The VD3 receptor is found in several cell types within the immune system, including macrophages, antigen presenting cells, Th1, Th2, and regulatory CD4⁺ T cells. VD3 directly inhibits the proinflammatory cytokines interleukin (IL) 2, IL-17, and interferon γ secreted by T cells, and attenuates cytotoxic activity and proliferation of T cells and B cells, thereby making itself a regulator of adaptive immunity.^{14,15} VD3 also affects innate immunity through the promotion of cathelicidin production by the sinonasal mucosa; cathelicidin encodes for the only antimicrobial peptide produced by humans.¹⁶ In addition to its antimicrobial function on mucosal surfaces, cathelicidin is a regulator of the local inflammatory response and chemoattraction.¹⁷ In addition, VD3 downregulates major histocompatibility complex class II expression on antigen presenting cells. Inhibiting antigen presenting cell maturation dampens the innate immune response, which further implicates VD3 in innate immune regulation.¹⁸

The ability of VD3 to augment innate and adaptive immune responses has sparked interest in its immunologic role in allergy. Results of recent studies indicate that VD3 plays a significant role in maintaining skin integrity, reducing pathogenic colonization, and dampening sensitization in atopic dermatitis.¹⁹ Similarly, Yenigun *et al.*²⁰ found a significant relationship between low VD3 levels in patients with allergic rhinoconjunctivitis compared with healthy controls. This relationship has also been validated in patients with asthma.²¹ Increasing evidence indicates that VD3 plays an important role in CRS and, therefore, may offer a therapeutic option. This review aimed to analyze the relationship among serum VD3 levels, CRS phenotype, and disease severity.

METHODS

Search Strategy

A systematic search was performed by using the PubMed, MEDLINE, and EMBASE databases. The PubMed database was searched from inception until May 15, 2015; EMBASE was searched from 1974 to May 15, 2015, and MEDLINE was searched from 1946 to May 15, 2015 by using Ovid SP. Bibliographies of studies selected for full-text analysis were reviewed for studies missed by

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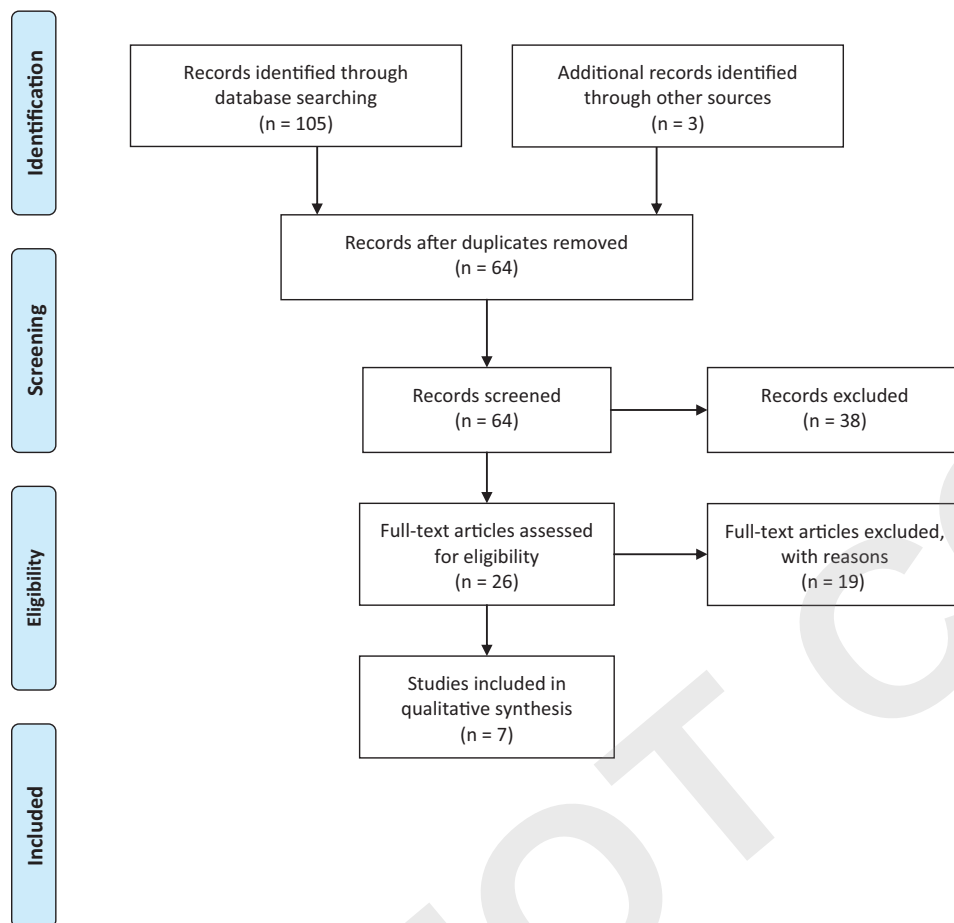


Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. From: Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 6:e1000097, 2009.

the search strategy. An electronic search strategy (see Supplemental Appendix 1) was designed to include all studies concerning the analysis of VD3 in CRS.

Eligibility Criteria

Inclusion and exclusion criteria were predefined. Only English language, human epidemiologic studies that measured serum VD3 levels of participants and that correlated the measurements to any subtype of CRS were included. Only studies with a measurement of the serum VD3 level were included because serum VD3 level is the most robust measurement of VD3 status. Existing reviews, letters to the editor, conference presentations, and other comments were included if they contained adequate data. Studies were excluded if they used VD3 estimates from questionnaires, if participants were supplemented with VD3, or if the studies were *in vitro* or animal model studies.

Study Selection

Two unblinded (P.S and J.R.) reviewed the titles and abstracts, read full-text articles that met the inclusion criteria, and extracted the relevant data by using a standardized data form. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram for study selection is shown in Fig. 1.

Data Collection

The following information was extracted from each included study: author(s), country, study design and duration, number of participants, inclusion and exclusion criteria, age, comorbidity, race, method of VD3 measurement, stated outcome measures, and

key results. Outcome measures considered relevant to the review included:

- Quantitative analysis of serum VD3 levels in CRS subtypes
- Degree of local inflammation: microscopic (inflammatory cells and/or biomarkers within sinonasal tissue) and macroscopic (computed tomography scoring)
- Degree of systemic inflammation: serum inflammatory biomarkers
- The data were summarized separately according to the following outcomes: (1) the association of serum VD3 with different CRS subgroups, (2) the association between serum VD3 and local inflammation, and (3) the association between serum VD3 and systemic inflammation.

RESULTS

Search Strategy

A total of 107 articles were identified by the search. Of these articles, 72 were excluded after screening the abstract. The full texts of the remaining 25 articles were reviewed, with 18 publications excluded because they did not meet the inclusion criteria. Seven articles were included in the final review^{22–28} (four prospective and three retrospective studies), with a total of 513 patients. However, five of the studies were from the same group,^{22–26} and, therefore, it is highly likely that the same patients were included in more than one study.

The characteristics of the included studies are shown in Table 1. Demographic details and efforts to control confounding variables were incompletely recorded. This final group of studies included one study of patients entirely with CRSwNP,²³ two mixed cohort studies

Table 1. Included studies for review

Study, y	Method	Participants	Outcomes Measured	Confounding Variables	Results
Pinto <i>et al.</i> , ²⁷ 2008	Prospective case-control study	154 subjects: 86 CRSwNP, 68 controls	VD3 levels; Harvard Staging CT scores	Race, age, sex, BMI, season	Lower serum VD3 levels in African Americans with CRS compared with race-matched controls ($p = 0.018$)
Mulligan <i>et al.</i> , ²⁴ 2011	Retrospective case-control study	57 subjects: 9 CRSwNP, 20 CRSsNP, 14 AFRS, 14 controls	VD3 levels; circulating immune cells (CD86 ⁺ monocytes, CD209 ⁺ DC and CD1c ⁺ DC), inflammatory markers (PGE2 ⁺ GM-CSF)	Race, atopic status, sex, age, CRS subtype (AFRS, CRSsNP, CRSwNP), season	Lower VD3 levels associated with CRSwNP and AFRS ($p < 0.0001$), inverse relationship between circulating DCs and VD3 levels ($p < 0.0001$), lower VD3 associated with more severe CT bony changes ($p = 0.016$)
Mulligan <i>et al.</i> , ²⁶ 2012	Retrospective case-control study	50 pediatric subjects: 5 CRSwNP, 17 CRSsNP, 14 AFRS, 14 controls	VD3 levels, local DC markers (CD209), co-stimulatory molecules (CD80 and CD86)	Race, asthma, atopy, sex, age, CRS subtype (AFRS, CRSsNP, CRSwNP)	Lower VD3 levels associated with CRSwNP ($p < 0.05$), AFRS ($p = 0.0018$), and increased mucosal DCs ($p < 0.01$)
Wang <i>et al.</i> , ²⁸ 2013	Prospective case study	45 subjects: 25 CRSwNP, 20 CRSsNP	VD3 levels; LM CT scores; polyp grade	Sex, BMI, asthma and/or atopic status, CRS subtype (CRSsNP, CRSwNP)	Lower VD3 levels associated with CRSwNP ($p < 0.001$), lower VD3 levels correlated inversely with polyp grade ($p < 0.001$)
Mulligan <i>et al.</i> , ²⁵ 2014	Prospective case-control study	106 subjects: 45 CRSwNP, 40 CRSsNP, 21 controls	Serum and sinonasal tissue VD3 levels, HSNEC VD3 gene expression; HSNEC 25-V _{D3} conversion to active 1,25-V _{D3} ; HSNEC cytokine production	CRS subtype (CRSsNP, CRSwNP), cigarette smoking	Lower mucosal ($p = 0.0145$) and serum ($p < 0.0001$) VD3 levels associated with CRSwNP; downregulation of 25V _{D3} -1- α -hydroxylase gene in CRSwNP ($p = 0.04$)
Schlosser <i>et al.</i> , ²³ 2014	Retrospective case study	70 subjects: 49 CRSwNP, 21 AFRS	VD3 levels; LM CT scores	Race, asthma, atopy, CRSwNP subtype (AFRS, AERD, CRSwNP)	Lower VD3 levels associated with African American race ($p = 0.028$) and worse LM score ($p = 0.007$)
Sansoni <i>et al.</i> , ²² 2015	Prospective case-control study	57 subjects: 31 CRSsNP, 14 CRSwNP, 12 controls	Serum VD3, mucus inflammatory markers (bFGF, RANTES, MCP-1)	Age, sex, comorbidities (COPD, obesity, smoking, diabetes), CRS subtype (CRSwNP, CRSsNP)	Lower VD3 levels in CRSsNP only ($p < 0.0001$); VD3 level negatively correlates with local mucus RANTES and bFGF concentrations in CRSwNP ($p < 0.05$)

CRSwNP = chronic rhinosinusitis with nasal polyp; VD3 = 25 hydroxyvitamin D; CT = computed tomography; BMI = body mass index; CRS = chronic rhinosinusitis; CRSsNP = chronic rhinosinusitis without nasal polyp; AFRS = allergic fungal rhinosinusitis; DC = dendritic cell; PGE2 = prostaglandin E2; GM-CSF = granulocyte macrophage colony-stimulating factor; LM = Lund-Mackay; HSNEC = human sinonasal epithelial cell; AERD = aspirin exacerbated respiratory disease; bFGF = basic fibroblast growth factor; RANTES = regulated on activation normal T expressed and secreted; MCP-1 = monocyte chemoattractant protein-1; COPD = chronic obstructive pulmonary disease.

of CRSsNP and CRSwNP,^{25,28} and four studies that compared CRS subtypes and controls.^{22,24,26,27}

Exposure Measurements

The method of measuring serum VD3 concentration varied among the studies. Three studies used enzyme immunoassay,^{22,24,25} two used liquid chromatography,^{23,26} and one used chemiluminescence assay.²⁸ The measurement tool used by Pinto *et al.*²⁷ was not clearly stated. There was heterogeneous reporting of VD3 sufficiency, insufficiency, and deficiency. Only four studies gave clear definitions for VD3 deficiency and

insufficiency.^{22–24,28} All these studies reported insufficiency as <30 ng/mL and deficiency as <20 ng/mL, except for Mulligan *et al.*,²⁴ who reported insufficiency as <32 ng/mL. In two other studies by the same researchers, there was either no definition given for VD3 deficiency,²⁵ or it was erroneously stated that insufficiency was <20 ng/mL and deficiency was <30 ng/mL.²⁶ Pinto *et al.*²⁷ provided no clear definition.

Outcomes

Studies assessed and defined CRS differently by using guidelines and tools. Five studies defined CRS according to consensus guide-

lines. Two studies used the most recent iteration of the European Position Paper on Rhinosinusitis and Nasal Polyps,^{23,25} one used the 2007 version,²⁸ and another used the 2007 Multidisciplinary Sinusitis Guidelines.²² Pinto *et al.*²⁷ stated “consensus diagnostic criteria” but did not specify their source. Two studies diagnosed CRS based on their own clinical and radiographic findings.^{24,26} Of the three articles that included eosinophilic (or allergic) fungal rhinosinusitis (EFRS), two used the Bent Kuhn criteria for diagnosis,^{24,26} whereas the third article failed to define EFRS, instead incorporated them into the CRSwNP group.²²

All seven studies correlated VD3 levels with CRS phenotypes. Severity of CRS was indirectly measured *via* local or systemic inflammatory markers in six studies.^{22–26,28} Locally, this included inflammatory cells or mediators within the sinonasal mucosa^{25,26} or mucus,²² and the degree of bone remodelling on radiographic imaging.^{23,24,28} The systemic inflammatory response was measured *via* serum biomarkers.^{24,28}

Confounding Variables

Age, sex, race, body mass index, atopic status, and seasonal variation were all identified from the literature as important potential confounders of the association between VD3 and CRS. Of the seven included studies, five adjusted or matched serum VD3 for age, sex, and race^{23,24,26–28}; four for body mass index^{23,24,27,28}; four for atopic status^{23,24,26,28}; and three for seasonal variation.^{24,27,28} Two studies made no reference to standardization of variables. Mulligan *et al.*²⁵ collected demographics of age, sex, and race but made no reference to whether their analysis accounted for these variables. Sansoni *et al.*²² noted age and sex but did not elaborate on the significance of these data. Underreporting of oral VD3 supplementation and patient comorbidities, including diabetes, chronic obstructive pulmonary disease, and autoimmune disease, may also have confounded the data.

Prevalence of VD3 Deficiency in CRS Subtypes

All seven articles analyzed the prevalence of VD3 deficiency in patients with CRS.^{22–28} Of these studies, five came from the Medical University of South Carolina group.^{22–26} The largest study from this center examined the association between serum VD3 levels, CRS subtype, cigarette smoking, and local regulation of VD3 in 164 patients.²⁵ Mulligan *et al.*²⁵ found significantly lower VD3 levels in patients with CRSwNP, regardless of smoking status, compared with patients with CRSsNP and control subjects. This was confirmed in two smaller, cross-sectional, case-control studies conducted by the same research group in 57 adult²⁴ and in 50 pediatric patients,²⁶ which compared VD3 levels in CRS subtypes and control subjects. Both studies showed significantly lower VD3 levels in CRSwNP and EFRS compared with CRSsNP and controls, independent of race, age, sex, and atopic status. A prospective cross-sectional study of 45 Taiwanese patients with CRS showed significantly lower VD3 levels in CRSwNP compared with CRSsNP.²⁸ One study alone found higher levels of VD3 in CRSwNP compared with CRSsNP and control cohorts, albeit without controlling for confounding variables.²²

Two articles analyzed racial interplay in VD3 deficiency and CRS subtypes. A review of 70 patients with CRSwNP found significantly lower VD3 levels in African American patients with CRSwNP compared with race-matched control subjects.²³ This was noted previously by Pinto *et al.*²⁷ who showed significantly lower serum VD3 levels in African Americans with CRS compared with race- and sex-matched controls.

VD3 Deficiency and CRS Severity

Local Inflammation. Three studies investigated the association between serum VD3 levels and sinonasal inflammation in CRS subtypes.^{22,25,26} Sansoni *et al.*²² analyzed serum VD3 levels and the concentrations of the proinflammatory molecules basic fibroblast growth

factor, regulated on activation normal T expressed and secreted (RANTES) and monocyte chemoattractant protein-1 in the mucus of 57 subjects. They concluded that lower VD3 levels were inversely related to local production of basic fibroblast growth factor and RANTES in CRSwNP. A cross-sectional study of 50 pediatric patients correlated serum VD3 levels with surgical mucosal biopsy specimens from patients with CRSwNP, patients with CRSsNP, and controls.²⁶ Lower serum VD3 levels were associated with elevated dendritic cell levels in the sinus mucosa on microscopic evaluation in subjects with CRSwNP and subjects with CRSsNP. Another study conducted with an adult population by Mulligan *et al.*²⁵ found that the gene encoding for 25-VD3-1 α -hydroxylase 25-VD3, the enzyme required for the conversion to the active form of VD3 (1,25-VD3), was significantly downregulated in the sinonasal mucosa of patients with CRSwNP compared with patients with CRSsNP and controls. Furthermore, they found that activated 1,25-VD3 blocked local proinflammatory cytokine production induced by cigarette smoke exposure.

Three cross-sectional studies assessed computed tomography (CT) severity scoring and VD3 levels in patients with CRS.^{23,24,28} Two scoring systems were used, the Lund-Mackay score (LMS)²⁹ and an adapted version for EFRS.³⁰ Two studies found a significant relationship between VD3 levels and bone remodeling on CT.^{23,24} Mulligan *et al.*²⁴ by using the adapted CT scoring system, found a significantly increased CT bone remodeling score in patients with insufficient levels of serum VD3 compared with adequate levels of serum VD3. There was a strong inverse relationship between reduced plasma VD3 levels and CT severity scoring. Schlosser *et al.*²³ by using the traditional LMS, found higher LMS in patients with lower VD3 levels when controlling for race, atopic status, and CRS subtype (EFRS). Wang *et al.*²⁸ found more severe polyp grades on radiographic examination in patients with lower VD3 levels, although there was not a significant correlation between VD3 levels and LMS.

Systemic inflammation. Two studies analyzed the effect of serum VD3 levels on systemic markers of inflammation.^{24,28} Mulligan *et al.*²⁴ showed that lower VD3 levels were associated with significantly increased CD209⁺ dendritic cells and the dendritic cell regulatory products prostaglandin E2 and granulocyte-macrophage colony-stimulating factor, all of which are systemic inflammatory markers. However, Wang *et al.*²⁸ were unable to find a significant relationship among CRS, serum VD3, and prostaglandin E2 levels.

DISCUSSION

This systematic review addressed the relationship between serum VD3 and CRS. It supported a role for VD3 in the pathophysiology of CRS, although the exact nature of this remains unclear. Most studies^{23–28} that investigated VD3 status in CRS found a significant association between lower VD3 levels and polypoid CRS phenotypes (CRSwNP and EFRS). Only one study did not identify a relationship between low VD3 and CRS, and, in fact, found a higher serum VD3 level in patients with CRSwNP compared with patients with CRSsNP and controls.²² However, the researchers conceded a failure to control for patient comorbidities likely influenced this result. Even so, a significant relationship between lower VD3 levels and a severe local inflammatory response within the mucus of subjects with CRS was noted.

These results validated findings of *in vitro* studies. Topical application of VD3 analogues (calcitriol and tacalcitol) to nasal polyp fibroblast cultures significantly decreased their proliferation.³¹ Two further studies found that topical VD3 reduced the synthesis of the proinflammatory cytokines IL-6 and IL-8, and influenced proapoptotic genes and pathways.^{32,33} It was reported that VD3 analogues decreased the *in vitro* secretion of RANTES and eotaxin, both potent eosinophil-specific chemokines, in nasal polyp fibroblast cultures.^{34,35} In addition, the effect of budesonide in RANTES and nasal polyp fibroblast culture proliferation suppression was potentiated by topical VD3 analogues, which indicates a potential role for dual ther-

apy.^{35,36} In terms of immunomodulation, sinonasal epithelial cell cultures can produce their own VD3 locally.¹⁶ Furthermore, the topical application of VD3 stimulated the expression of cathelicidin, a gene that encodes for antimicrobial peptides important for epithelial immunity. These findings alluded to a role for VD3 in augmenting the innate local immune response within the sinonasal mucosa.

Only one study attempted to assess whether VD3 has a therapeutic effect in patients with CRS; this study was excluded from the review due to inadequate outcome measurements.³⁷ Cod liver oil and VD3 (within a multivitamin preparation) were given as an adjunctive therapy to four pediatric patients with chronic or recurrent sinusitis, starting at a dose of 3750 IU/day of vitamin A and 700 IU/day of VD3.³⁷ The option of dose escalation, to 7500 IU/day vitamin A, 1400 IU/day VD3, and 3 g/day of fish oil, was given to the patients' parents after a defined period. It was reported that patients had decreased sinus symptoms, fewer episodes of acute sinusitis, and fewer physician visits for acute illnesses. This study had several vulnerabilities that involved its size and study design.³⁷ Confounding variables, including the type and frequency of concomitant antibiotic and steroid treatment, may have impacted the results. Furthermore, the outcome measurements of the study were based on questionnaires and the subjective measurements of symptoms by the parents; because no serum VD3 levels were measured, it is impossible to accurately deduce the VD3 status of each child.³⁷

Heterogeneous reporting of exposure measurements, outcomes, and confounding variables among the included studies precluded meta-analysis, in addition to the likely significant overlap of the subjects included in three of the studies from the same group over the same time period.^{23–25} The definition of CRS varied among studies; several guidelines and tools were used to diagnose CRS cohorts, whereas some studies^{24,26,27} made the diagnosis based on their own clinical and radiographic findings. There was no standardized method of collection and analysis of serum VD3, and there was no consensus within the literature on what VD3 level constitutes "healthy" and what quantitative thresholds can be applied to sufficiency, insufficiency, and deficiency.^{10,38–40} Normal VD3 is based on values that correlate with bone health, the most well-detailed function of VD3. Results of recent research indicate that these values do not assimilate evenly to general health and may even be too low.²¹

The analysis of VD3 and CRS severity was difficult because the outcome measurements differed for each study. Serum VD3 levels were compared with varying local inflammatory markers and cytokines in tissue²⁶ and mucus²² as well as with different systemic inflammatory markers.²⁸ Two different CT scoring systems (Lund Mackay²⁹ and an adapted version by Wise³⁰) were used in the three studies concerned with bone remodelling.^{23,24,28} Confounding variables were inconsistently reported and accounted for, which included the seasonal exposure of VD3 that was mentioned in only three of the seven studies. Important exclusion considerations, including VD3 supplementation, corticosteroid use, and other comorbid diseases, associated with low serum VD3 were only intermittently reported.

The retrospective designs of several included studies inevitably resulted in a number of shortcomings. It was impossible to deduce temporal associations between serum VD3 and CRS due to the cross-sectional nature of these articles. It could be hypothesized that patients with CRS avoid going outdoors so to reduce their symptoms and, therefore, have lower VD3 levels because of this. It has also been noted previously that VD3 acts as a negative acute phase reactant and that the inflammation of CRS itself may decrease VD3 levels.²¹ The retrospective nature of the studies exposes them to selection and reporting bias. Two studies failed to state whether their outcome assessors were blinded to exposure measurements.^{25,28}

CONCLUSION

Despite the limitations of the epidemiologic study designs and inconsistent reporting of important details among the included stud-

ies, this review indicated that there is an association between serum VD3 and CRS. Low serum VD3 is more prevalent in patients with CRSwNP and in patients with EFRS, although no definitive conclusion can be made on whether VD3 is a causative factor in CRS, nor can VD3 contribution to severity be quantified. The conclusions drawn in this review supported previous work on the role of VD3 in respiratory disease.^{14,41} The review by Yawn *et al.*⁴¹ similarly mentioned that it would be premature to make any claims about the therapeutic role of VD3 in CRS given the retrospective nature of the included studies and the lack of VD3 supplementation studies in the current literature.

To further substantiate the role of VD3 in CRS, there is a requirement for longitudinal studies and/or randomized control trials to extrapolate these data and minimize bias. Ideally, future studies would use standardized outcome measures and methods of VD3 measurement. Prospective longitudinal studies, which look toward future randomized controlled trials, will, it is hoped, help to clarify the relationship between VD3 and CRS, and identify a role, if any, for VD3 supplementation in the treatment of CRS.

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