

Original Research Article

A study to evaluate the relationship between serum vitamin d level and chronic rhinosinusitis

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ABSTRACT

Background: Chronic rhinosinusitis (CRS) places a relatively large socioeconomic burden on developed nations, yet remains a difficult disease to treat. Vitamin D3 (VD3) deficiency is reported to be associated with increased incidence of allergic airway diseases. The ability of VD3 to augment innate and adaptive immune responses has sparked interest in its immunologic role in allergy. The objective of the present study is to evaluate the relationship between serum vitamin D level and chronic rhinosinusitis.

Methods: Total 90 patients were included in the study and divided into three groups i.e., 30 patients of chronic rhinosinusitis with nasal polyposis (CRSwNP), 30 patients of chronic rhinosinusitis without nasal polyposis (CRSSNP) and 30 healthy subjects were used as control. The severity of CRSwNP was assessed with the Lund-Mackay (LM) score and polyp grading system. VD3 status was assessed by measuring circulating 25-hydroxyvitamin D (25OHD) by using ELISA.

Results: Serum 25OHD levels (ng/ml±SD) were significantly lower in patients with CRSwNP (16.16±8.86) than in those with CRSSNP (23.28±5.35; p=0.001) and control 44.37±19.87. The incidence of vitamin D deficiency (<20 ng/ml) in CRSwNP and CRSSNP patients were 60% and 20%; however, the incidence of vitamin D insufficiency (20-30 ng/ml) in these patients were 37% and 70%, respectively. A significantly inverse relationship was found between serum 25OHD level and polyp grade (p=0.048), indicating lower serum 25OHD was associated with higher polyp grade. Serum 25OHD was inversely related to both LM endoscopic and LM CT scan score, which is found to be significant (p=0.001).

Conclusions: The available evidence indicates that there is a significant relationship between low VD3 levels and CRSwNP phenotype. Lower 25VD3 levels were associated with more severe mucosal inflammation on nasal endoscopy and CT scan.

Keywords: Chronic rhinosinusitis, Vitamin D3, Lund-Mackay score, Nasal polyposis, Enzyme linked immunosorbent assay

INTRODUCTION

Chronic rhinosinusitis (CRS) is a disease of the upper respiratory tract characterized by diffuse inflammation of the sinonasal mucosa.¹ CRS is a significant health problem whose incidence and prevalence is rising. CRS remains difficult to treat in many cases and represents a

large socioeconomic burden. It is one of the most prevalent chronic diseases worldwide.²

CRS is a multifactorial disease with unknown etiologic and pathophysiologic aspects. The proposed etiologies for this disease include anatomic factors, infectious

causes, fungal allergies, immunological disorders, biofilms, and genetic causes.³

However the current theories of pathogenesis of CRS include super antigen, and immune barrier hypotheses, which describe a balance of interactions among the host, commensal flora, potential pathogens, and exogenous stresses.⁴ The current evidence supports two predominant immune phenotypes in CRS that arise secondary to skewing of the T helper (Th) cells. CRS without nasal polyposis (CRSsNP) is Th1-skewed whereas CRS with nasal polyposis (CRSwNP) is Th2-skewed. One of the recently proposed factors that may have some roles in the pathophysiology of CRS is 25-hydroxyl vitamin D (OH-VitD) deficiency.⁵

Recently, there has been a focus on the nonskeletal effects of VD3, including cardiovascular, autoimmune and immunomodulatory roles.^{6,7} Now VD3 is considered to have an immunomodulatory role, especially in allergic diseases.⁷ Low serum VD3 level in the body is now considered as a risk factor for many immune-linked diseases such as allergic diseases-for example, asthma and recurrent upper respiratory tract infection.⁸ VD3 plays an important role in inflammatory diseases such as CRS. Active VD3 causes cellular responses by binding to an intracellular VD3 receptor, which act as a ligand-dependent transcription factor that affect the expression of various genes. The VD3 receptors 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 pro-inflammatory cytokines interleukin IL-2, IL-17, and IFN- 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.^{9,10} VD3 also affects innate immunity through the promotion of cathelicidin production by the sinonasal mucosa, cathelicidin encodes for the only antimicrobials produced by the humans.¹¹ VD3 downregulates major histocompatibility complex (MHC) class II expression on antigen presenting cells maturation dampens the innate immune response which further implicates VD3 in innate immune regulation.¹² VD3 status is determined by measuring the serum concentration of 1.25(OH)2D, the major circulating form of the hormone measured by ELISA.¹³ The ability of VD3 to augment innate and adaptive immune responses has sparked interest in its immunologic role in allergy. VD3 deficiency may also contribute to bone erosion in CRS.

The present study is aimed to determine the relationship between CRS and serum VD3 levels. Therefore whether VD3 deficient patients are at risk for developing CRSwNP and CRSsNP and correlation of VD3 levels with severity of clinical symptoms, radiological findings of mucosal inflammation.

Objectives

- To evaluate the relationship between serum VD level and chronic rhinosinusitis.
- To determine whether VD3 deficient patients are at risk for developing CRSwNP (chronic rhinosinusitis with nasal polyposis) and CRSsNP (chronic rhinosinusitis without nasal polyposis).
- To determine correlation of VD3 levels with severity of clinical symptoms, radiological findings of mucosal inflammation.

METHODS

The present prospective and observational study was conducted from July 2016 to August 2018 in the Department of ENT, Rajindra Hospital, Patiala on 90 subjects divided into three groups as CRSwNP (30 patients), CRSsNP (30 patients) and control group (30 subjects) diagnosed by the widely accepted definition developed by the American Academy of Otolaryngology-Head and Neck Surgery adult sinusitis guidelines. The inclusion criteria included patients of both sexes with age ranged from 18 to 55 years. Informed written consent was taken from every patient to participate in study. Exclusion criteria included pregnancy, patients taking multivitamins containing vitamin D for atleast 6 months, Patients on systemic steroids or non-steroidal anti-inflammatory agents, for at least three months. Patients having underlying diseases such as rheumatoid arthritis, immunodeficiency or cystic fibrosis, rickets, osteoporosis, control group of patients having history of sinusitis, radiographic and endoscopic evidence of inflammation of sinuses and patient with recurrent nasal polyposis after previous sinus surgery. A detailed history was taken and proforma was filled up. Each patient was subjected to detailed clinical examination, anterior and posterior rhinoscopy and diagnostic nasal endoscopy and neck nose and paranasal sinuses. Levels of VD3 were measured by enzyme linked immunosorbent assay (ELISA). VD3 insufficiency was defined as 20-30 ng/ml and deficiency as <20 ng/ml. Symptom, endoscopic and radiological score was done by using Lund and Mackay staging system.

Statistical analysis

All of the statistical analyses were performed with the IBM SPSS 22 version. Descriptive statistics were given as the arithmetic mean \pm standard deviation (SD). For comparing the values of the two different groups, we used t-test and Spearman's Rho. A value of $p < 0.05$ was considered statistically significant.

RESULTS

As per demographic data of the study population there were no significant differences between groups regarding age, sex and location (Table 1). Area wise distribution of study subjects was given in Table 2.

Table 1: Demographic data.

	CRSwNP (n=30)	CRSSNP (n=30)	Control (n=30)	P value
Sex (male/female)	9/21	16/14	15/15	0.148
Age (mean, years)	35.67±11.24	32.50±11.82	34.80±8.59	0.495
VD3 (mean± SD, ng/ml)	16.16±8.86	23.28±5.35	44.37±19.87	0.001

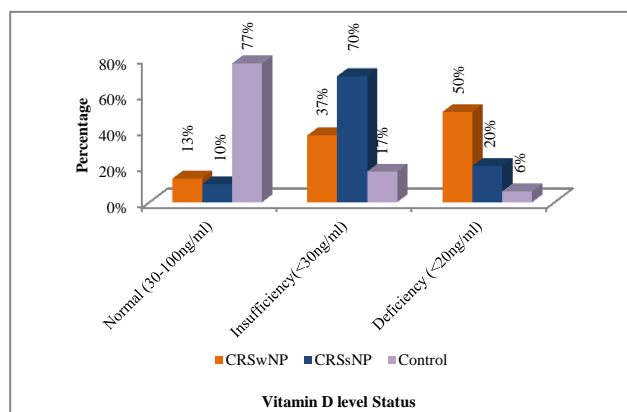
Table 2: Distribution of study subjects based on location.

Location	CRSwNP (n=30) N (%)	CRSSNP (n=30) N (%)	Control (n=30) N (%)
Rural	12 (40)	20 (67)	22 (73)
Urban	18 (60)	10 (33)	8 (27)
Total	30 (100)	30 (100)	30 (100)

Mean serum VD3 levels for CRSwNP 16.16±8.86 were significantly lower when compared to either control (23.28±5.35) or CRSSNP (44.37±19.87), ($p=0.001$). Vitamin D status; deficient levels were found in 60% of CRSwNP group, 20% of CRSSNP and 6% in control group. Insufficient levels were found in 37% of CRSwNP, 70% of CRSSNP and 17% of control groups whereas normal levels were found in only 3% in CRSwNP, 10% of CRSSNP and 77% of control groups (Table 3).

Table 3: Serum VD3 level in different groups.

Vitamin D Status	CRSwNP (n=30) N (%)	CRSSNP (n=30) N (%)	Control (n=30) N (%)
Normal (30-100 ng/ml)	3	10	77
Insufficiency (<30 ng/ml)	37	70	17
Deficiency (<20 ng/ml)	60	20	6

**Figure 1: Serum VD3 status (ng/ml).**

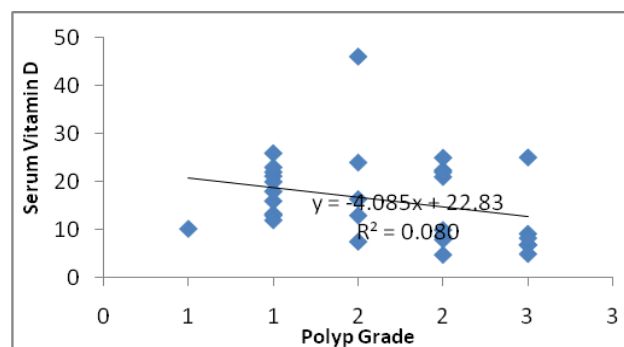
Significant inverse relationship was found in serum VD3 levels of CRSwNP group and LM scoring ($p=0.001$) and the relationship of VD3 level with LM scoring of CRSSNP group was found to be non-significant ($p=0.937$) (Table 4). In the present study we found that the serum vitamin D level was inversely related to polyp grade (Spearman's $Rho=-0.363$), which was found to be statistically significant ($p=0.048$) (Table 5).

Table 4 Relationship between VD3 levels and LM scoring.

	Serum VD3	LMES	LMCTSS	P value
CRSwNP	16.16±8.86	8.00±2.44	14.80±4.87	0.001
CRSSNP	23.28±5.35	4.00±1.55	5.87±3.30	0.937

Table 5: Relationship between polyp grade and serum VD3 level in patients with CRSwNP.

Polyp grade	Patients N (%)	VD3	P value (Spearman's Rho)
Grade 0	0 (0)	0.00	0.048 (-0.363)
Grade 1	11 (36.67)	17.69	
Grade 2	13 (43.33)	17.59	
Grade 3	6 (20)	10.22	

**Figure 2: The relationship between serum VD3 level and polyp grade.**

DISCUSSION

CRS has a significant impact on quality of life, with symptom severity comparable with classically debilitating diseases such as congestive heart failure,

chronic back pain, and chronic obstructive pulmonary disease.^{1,14} The literature suggests that CRSwNP increases with age, with a mean onset across all ethnic groups of 42 years.¹⁵⁻¹⁷

VD3 deficiency, in particular, has been linked to a high rate of both infectious and inflammatory diseases, including those of the upper and lower airways, such as rhinosinusitis, pneumonia, influenza A, and otitis media.¹⁸

The role of VD3 in pathogenesis of CRSwNP is now just beginning to be better understood. It appears that sinonasal epithelial cells express 1- α -hydroxylase and can produce 1,25(OH)₂ VD3 locally. Absence of this molecule leads to the reduced antibacterial response, increased release of inflammatory cytokines and increased fibroblast proliferation in patients with CRSwNP.¹⁹

The age of the patients in all the three groups ranged from 18-55 years. Maximum number of study subjects were in the age group of 26-35 years. Mean age in CRSwNP group was 35.67 \pm 11.24 and in CRSsNP group was 32.50 \pm 11.82. While in the control group, mean age was 34.80 \pm 8.59. A study done by Wang et al (2013) reported mean age of the patients with CRSwNP was 45.63 years and in patients with CRSsNP was 54.04 years.²⁰ A similar study done by Mulligan et al reported that mean age of patients with CRSwNP was 38 \pm 17 years, in patients with CRSsNP was 49 \pm 20 years and in control group was 48 \pm 19.²² These studies are in accordance with our findings that the incidence of CRSwNP increases with the age, mean age of onset being 42 years.

In the present study there was female preponderance, out of 60 patients, 35 (58%) were females and 25 (42%) were males. Male to female ratio was found to be 1:1.4. A study done by Sansoni et al (2015), there were 26 (45.6%) males and 31 (54.5%) females.²² A study done by Sedaghat et al (2015), there were 59.2% females and 40.2% males.²³ In our area most of the females are housewives and they mostly remain indoor which might be the reason for low vitamin D levels as well as increased incidence of CRSwNP.

In CRSsNP group, 67% patients belonged to the rural area and 33% belonged to urban area. Whereas in CRSwNP group more patients belonged to urban area (60%) than in the rural area (40%). As per data in the present study, incidence of CRSwNP is higher in urban areas. This may be attributed to decreased outdoor activities, obesity, and excessive use of sunscreen in present day urban population which leads to low levels of VD3 as well as higher incidence of CRSwNP.²⁴

In the present study serum vitamin D levels were evaluated in all ninety patients and compared in each group. Serum vitamin D insufficiency was defined as <30 ng/ml and deficiency defined as <20 ng/ml. In the present study the incidence of vitamin D deficiency (<20 ng/ml)

in CRSwNP and CRSsNP patients were 60% and 20%; however, the incidence of vitamin D insufficiency (20-30 ng/ml) in these patients were 37% and 70%, respectively. A prospective study by Mostafa et al 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.²⁵ A recent study by Habibi et al 2019 also showed the serum VD3 levels were lower in CRSwNP group than in CRSsNP group.⁵ The present study is in accordance with the previous studies in view of serum vitamin D levels in different groups. There is evidence that VD3 acts directly on monocytes, macrophages, dendritic cells, and T cells similarly to steroids. Moreover, the VD3 deficiency seems to be implicated in the pathogenesis of CRSwNP.²⁶ All these studies support a role for VD3 as a key player in the immunopathology of CRSwNP.

Objective measures of CRS severity include radiographic staging and endoscopic scoring. The severity of CRS (CRSwNP and CRSsNP) was assessed with the Lund Mackay (LM) scoring system. VD3 deficiency may be associated with increased bone erosion or severity in CRSwNP. In the present study we found that there is inverse relationship between serum VD3 level and LMCT and LM endoscopic scoring ($p=0.000$). Schlosser et al (2014) also found that Lower VD3 levels correlated with more severe mucosal disease as measured by Lund-Mackay CT scoring.²⁷ Another study by Lordanis et al (2017) who also reported, that the LM CT scores were inversely correlated with the VD3 levels.²⁶ The results of CRS severity of previous studies are in accordance with the current study.

The severity of nasal polyp was assessed with the nasal polyp grading system described by Lund and Mackay. We evaluated that the VD3 level was inversely related to polyp grade ($p=-0.363$). Wang et al (2013) showed the inverse relationship between serum VD3 level and polyp grade, which is in accordance with the present study indicating that lower serum VD3 level was associated with higher polyp grade.²⁰

This study showed that serum VD3 levels in CRSwNP patients were significantly lower than those in patients with CRSsNP and control group. Serum VD3 level was significantly and inversely related to the polyp grade. The correlation of serum VD3 level to LM score also found to be statistically significant.

Hence vitamin D is used now as one of the new drugs for the treatment of allergic diseases besides its role in calcium homeostasis and bone mineralization.

Limitations

The limitations of the present study are: firstly the high cost of vitamin D test secondly some patients could not afford CT scanning and thirdly small sample size making it difficult to draw conclusions.

CONCLUSION

In this study we found that lower VD3 levels are associated with higher incidence of nasal polyposis and increased symptom severity. Serum VD3 level is found to be inversely related to polyp grade (Spearman's $Rho = -0.363$). This may result in more perpetuations of chronic inflammatory sinus diseases and supports the role of VD3 in the pathogenesis and degree of severity of nasal polyposis. The correlation of serum VD3 level to LM score was statistically significant in CRSwNP. Hence, if the vitamin D3 deficiency is corrected, the occurrence of nasal polyposis and increased symptom severity in chronic cases of rhinosinusitis should decrease. Therefore, the serum vitamin D assessment should be recommended as a routine investigation in all patients with CRS to determine the disease severity and hence decrease the morbidity related to symptom severity of chronic rhinosinusitis.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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