



2023

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### How to Cite This Article

Basha, Salem Ibrahim; Hassan, Ahmed Abdelbaset; Shaaban, Mostafa Mohamed; and Younis, Mohamed Abdelmoneam (2023) "Vitamin D3 and chronic rhinosinusitis, Is there a relationship?," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 4, Article 6.

DOI: <https://doi.org/10.58675/2682-339X.1747>

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# Vitamin D3 and Chronic Rhinosinusitis, Is There a Relationship?

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## Abstract

**Background:** One of the most prevalent conditions without a proven long-term treatment is chronic rhinosinusitis (CRS). There are two phenotypes of CRS: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP). Immunomodulation is thought to be a function of vitamin D (VD), particularly in allergic disorders.

**Objective:** This investigation was done to assess the link between blood VD3 levels and CRS, whether it had polyps or not.

**Patients and methods:** 90 people from both sexes participated in this study. Adults were divided into three categories and given the diagnosis of sinusitis by the American Academy of Otolaryngology Head and Neck Surgery: CRSsNP (30 subjects), CRSwNP (30 subjects), and control group (30 subjects). Using an ELISA (enzyme-linked immunosorbent assay), VD levels were measured (ELISA).

**Results:** The serum 25 (OH) D level varied between the CRSsNP Group ( $23.10 \pm 7.40$ ), CRSwNP Group ( $22.20 \pm 8.12$ ), and Control Group ( $26.22 \pm 8.25$ ). Regarding VD3, there was no discernible difference between the studied groups. Age-related differences across the groups were statistically significant, with CRSwNP being more prevalent in the older age group ( $55.07 \pm 5.78$ ). There was no discernible difference in symptomatology or sex.

**Conclusions:** CRS, whether it had polyps or not, did not correlate with serum vitamin D3 levels. This indicates that low levels of serum 25 (OH) D are not a potential risk factor for CRS in adult patients.

**Keywords:** 1- $\alpha$ -hydroxylase, HSNEC, Nasal polyps, Rhinosinusitis, Vitamin D3

## 1. Introduction

Chronic rhinosinusitis (CRS) is one of the most common illnesses affecting people around the world due to inflammation of the mucosal lining of the nose and nasal sinuses. No specific therapy can treat CRS in the long term, but various medications and modalities to control the disease and reduce it. Recent guidelines defined CRS depends on symptoms, endoscopic examination and radiological results.<sup>1</sup> CRS can manifest itself in a variety of ways as CRS without nasal polyps (CRSsNP) and CRS with nasal polyps, respectively (CRSwNP).<sup>2</sup> CRS is a complex illness whose aetiology and pathophysiologic characteristics are unknown. Anatomical factors,

pathogenic causes, allergies to fungi, immunological factors, biofilms, and genetic causes are some of the potential etiologies for this illness. However, explains how interactions between the host, commensal flora, possible pathogens, and foreign stimuli are balanced. Includes the immunological barrier and super antigen ideas, are currently accepted theories of the aetiology of CRS. The evidence at hand suggests that there are two immunological phenotypes that predominate in CRS and are caused by aberrant T helper (Th) cells. Unlike CRSwNP, which is Th2-aberrant, CRSsNP is Th1-aberrant. Deficiency in 25-hydroxyvitamin D (OH- VitD). It has been determined that one of the recently proposed factors that could play a part in the pathophysiology of CRS.<sup>3</sup>

Accepted 17 October 2022.

Available online 27 June 2023

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<https://doi.org/10.58675/2682-339X.1747>

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Traditionally, vitamin D was associated with bone mineralization, plasma calcium levels and bone deposition; however, today vitamin D is thought to play an immunomodulatory role, notably in allergic disorders.<sup>4</sup> Pro-vitamin D3 is converted non-enzymatically to pre-vitamin D3 in the epidermis as the first step in the production of vitamin D3. The enzyme 25-hydroxylase is found in the liver and promotes the conversion of pre-vitamin D3 to 25-hydroxyvitamin D3, which is the form that most closely resembles exposure from the skin and diet. 25-hydroxyvitamin D3 is ultimately transformed into its active metabolite, 1,25-dihydroxyvitamin D3 by the kidneys. However, other tissues, such as human sinonasal epithelial cells (HSNEC), also include functional 1- $\alpha$ -hydroxylase enzymes.<sup>5</sup> The relationship between persistent rhinosinusitis with or without polyps and serum vitamin D3 levels was examined in this study.

## 2. Patients and methods

Ninety patients of both sexes participated in this prospective study at Al Hussein University Hospital after receiving written informed permission and counselling regarding the study's purpose. Three sets of subjects, CRSwNP (30 subjects), CRSsNP (30 subjects), and control group were created (30 subjects).

### 2.1. The inclusion criteria

- (1) Patients of both sexes with age ranged from 18 to 55 years.
- (2) Patients having CRS with or without polyposis, diagnosed clinically, endoscopically and radiologically.

### 2.2. Exclusion criteria

Pregnancy, patients who have taken nonsteroidal anti-inflammatory drugs or systemic steroids for at least three months, individuals who have taken vitamin D-containing multivitamins for at least 6 months.

Individuals with underlying illnesses, including rheumatoid arthritis, rickets, osteoporosis, immunodeficiency, cystic fibrosis, the patients in the control group had recurrent nasal polyposis after prior sinus surgery, endoscopic and radiographic indications of sinus inflammation, and a history of sinusitis. A comprehensive history was gathered, and a questionnaire was filled out. An extensive clinical examination, diagnostic nasal endoscopy, and anterior

(Fig. 1) and posterior rhinoscopy were all performed on each patient, and a CT scan of the nose and paranasal sinuses (Fig. 2). Blood samples were drawn, centrifuged, and used to measure the levels of VD using an ELISA (enzyme-linked immunosorbent assay). VD deficiency was designated as 20 ng/ml, and VD insufficiency as 20–30 ng/ml.

## 3. Results

Age differences between the analysed groups were statistically significant ( $P = 0.01$ ), whereas sex differences were not statistically significant ( $P = 0.87$ ) (Table 1).

There was no significant difference between groups of the study regarding sign/symptom (Table 2).

There was no significant difference among groups of the study regarding serum vitamin D3 level (Table 3).

There was insignificant difference between studied groups as regard Vitamin D3 category (Table 4).

## 4. Discussion

An upper respiratory tract condition known as CRS is characterised by extensive sinonasal mucosa irritation.<sup>1</sup> The Symptoms can remain greater than 12 weeks.<sup>6,7</sup> CRS is strongly recommended as a

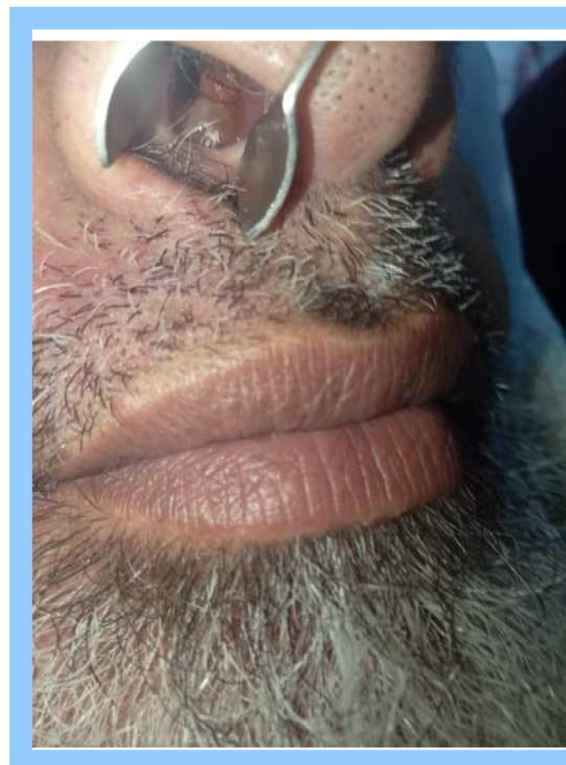


Fig. 1. Anterior rhinoscopy showing nasal polyps.



Fig. 2. CT nose and paranasal sinuses showing opacity of nasal cavity and entire sinuses.

medical disease in which surgery has an adjuvant therapeutic role after failure of maximal medical treatment. Important advances in medical and surgical techniques not only reduced morbidity but also improved long-term disease control.<sup>8</sup>

Vitamin D (Vitamin D3) has a long history of being recognised for its function in calcium homeostasis and bone mineralization. The nonskeletal effects of vitamin D3, such as its roles in the

cardiovascular, autoimmune, and immunomodulatory systems, have recently received attention.<sup>9</sup>

In the current investigation, there was an age difference between the groups that was statistically significant ( $P = 0.01$ ). Age on average for CRSsNP group, CRSwNP and Control was  $44.5 \pm 16.5$ ,  $55.07 \pm 5.78$  and  $49.5 \pm 14.8$  years, respectively. Zhang et al.,<sup>10</sup> reported that CRSsNP was the most common diagnosis in the young group and CRSwNP was the most common diagnosis in the middle-aged group and the old group ( $P < 0.05$ ). Holmes et al.,<sup>11</sup> in their study found that young adults had significantly greater sinonasal outcome test (SNOT-22) score, significantly greater rhinologic scores and significantly greater Lund-Kennedy (LK) endoscopy scores than the adult and aged patients.

The present study revealed statistically insignificant difference between the studied groups regarding Sex ( $P = 0.87$ ). Regarding gender, 40% were males and 60% females in group CRSsNP while in group CRSwNP, 43% were males and 57% females. Sex distributions were comparable among groups in the studies conducted by Christensen et al.,<sup>12</sup> and Habibi et al.,<sup>13</sup> which was in agreement with the present study.

According to the investigation's findings, there was no discernible difference between Sign and

Table 1. Demographic characteristics among studied groups.

	CRSsNP Group (n = 30) N (%)	CRSwNP Group (n = 30) N (%)	Control group N (%)	Test value	P value
Gender					
Male	12 (40%)	13 (43.0%)	14 (46%)	$\chi^2 = 0.27$	0.87
Female	18 (60%)	17 (57.0%)	16 (56%)		
Age (years)					
Mean $\pm$ SD	$44.5 \pm 16.5$	$55.07 \pm 5.78$	$49.5 \pm 14.8$	F = 28.02	0.01

P value < 0.05 is significant, P value < 0.01 is highly significant, SD: Standard deviation,  $\chi^2$  = Chi-Square test.

Table 2. Comparison between groups of the study regarding Sign/Symptom.

	CRSsNP Group (n = 30) N (%)	CRSwNP Group (n = 30) N (%)	Test value	P value
Facial Pain Pressure	25 (85)	21 (70)	1.491	0.22
Facial congestion	12 (40)	8 (25)	1.2	0.27
Nasal obstruction	18 (60)	21 (70)	0.6593	0.416
Purulent discharge	12 (40)	8 (28)	1.2	0.27
Hyposmia/anosmia	3 (10)	6 (20)	–	–
Purulence on examination	12 (40)	12 (40)	–	–
Fever (acute)	2 (7)	2 (7)	–	–
Headache	25 (85)	24 (80)	0.1113	0.73
Fever (nonacute)	2 (7)	3 (10)	0.2182	0.64
Halitosis	4 (14)	2 (6)	0.7407	0.38
Fatigue	1 (3)	3 (10)	1.071	0.30
Dental Pain	1 (3)	3 (10)	1.071	0.30
Cough	10 (33)	8 (25)	0.3175	0.57
Otalgia	1 (3)	2 (6)	0.3509	0.55

Table 3. Comparison among the studied groups regarding serum Vit D.

	CRSsNP Group (n = 30)	CRSwNP Group (n = 30)	Control Group	Test value	P value
VD3 (mean $\pm$ SD, ng/ml)	23.10 $\pm$ 7.40	22.20 $\pm$ 8.12	26.22 $\pm$ 8.25	47.15	0.62

Symptom. In contrast, CRSsNP patients often complain more about headaches and postnasal drip. A closer look at the symptom profiles reveals that CRSwNP patients frequently feel nasal obstruction and loss of smell. All CRS patients display a pattern of symptoms and indications that slightly overlap, according to Dietz et al. and Huvenne et al.<sup>14,15</sup>. There was no statistically significant difference in serum vitamin D3 levels across the study groups according to the current experiment. According to Schlosser et al.,<sup>16</sup> there were no statistically significant differences between the CRSsNP and CRSwNP control groups' serum 1,25VD3 levels. According to research by Lee et al.,<sup>17</sup> conducted in Korea, the circulating 25(OH) D level in the CRS group was higher than that in the control group (17.057 'plus or minus' 6.56 ng/ml,  $P = 0.0072$ ), at 19.293 'plus or minus' 7.035 ng/ml. In the study of Christensen et al.,<sup>12</sup> sinus mucosal samples from patients with CRSsNP and CRSwNP as well as a control group, quantitative polymerase chain reaction was used to analyse the genes for the vitamin D receptor (VDR), 25-hydroxylase (CYP2R1), 1-hydroxylase (CYP27B1), and 24-hydroxylase (CYP24A1). To change the expression levels, the Nasal Symptom Score, the 22-item Sinonasal Outcome Test (SNOT-22), and serum 25(OH)D [sum 25(OH)D2 and 25(OH)D3] were employed (NSS). Because there were no clear correlations between blood 25(OH)D levels and the expression of CYP2R1, CYP27B1, or CYP24A1 in the three groups examined, the researchers hypothesised that the local control of vitamin D in sinonasal tissue during CRS may not be dependent on serum levels. However, Li et al.,<sup>18</sup> discovered a strong correlation between CRS, namely CRSwNP, and lower blood vitamin D status in their meta-analysis. They emphasised that their study's limitations were comparable to those of other observational studies, though. For instance, only 8 research total, some of which weren't all that impressive, were included. There was a selection and recall bias because the majority of the included studies used a case–control design and were retrospective studies.

Second, the results of several studies varied. They revealed that the CRS phenotype may be the cause of variation in this meta-analysis through the evaluation of subgroups. Finally, because several of the studies were published in languages other than English, they rejected some of them that might have had insufficient data. Similarly, Bavi et al.,<sup>19</sup> a direct correlation between disease severity and vitamin D3 level was established in Iranian CRSwNP patients, it was determined. The amount of vitamin D3 in the blood may be impacted by a variety of factors, including skin colour, race, socioeconomic class, way of life, body mass index, dietary status, daytime sun exposure, sunscreen use and chronic liver and renal conditions. In terms of ethnicity, sex, age, and the absence of chronic diseases, they matched the study groups; however, they did not do so in terms of other characteristics that were evaluated and matched between groups. In the study by Mostafa et al.,<sup>20</sup> 74 participants were divided into 4 groups: group A included 25 patients with allergic fungal rhinosinusitis (AFRS); group B included 15 patients with CRS and nasal polyps (CRSwNP); group C included 15 patients with CRS without nasal polyps (CRSsNP); and group D included 15 patients without nasal polyps. and group D consisted of 19 controls. In contrast to the current investigation, there was a difference in the amount of circulating VD3 between groups A and B and groups C and D that was statistically significant ( $p < 0.001$ ). Uncertainty exists regarding the association between serum vitamin D3 and CRS either with or without polyposis, some researchers found low vitamin D3 in serum in cases of CRS especially with polyposis while others found no relationship. However, some other contributing factors might be responsible for the decrease of serum vitamin D3 as lack of sun exposure or other comorbide diseases that decrease the synthesis of vitamin D3 like bone and rheumatological diseases. Thus further investigations are recommended with exclusion of these contributing factors. Although most studies have shown that the serum vitamin D3 is not

Table 4. Comparison the studied groups regarding Vitamin D3 category.

Vitamin D3 category (ng/ml)	CRSsNP Group (n = 30)		CRSwNP Group (n = 30)		Control Group (n = 30)		Test value	P value
Deficient (<20)	8	27	10	33	7	23		
Insufficient (20–30)	18	60	19	63	17	57	3.223	0.19
Sufficient (>30)	4	13	1	3	6	20		

deficient in most of patients with CRS either with or without polyposis, some other recent studies found a deficient vitamin D in local Sinonasal tissue in cases of CRSwNP. Wynne et al.,<sup>21</sup> explained that the decrease in 1,25VD3 in CRSwNP is local not systemic due to reduced Sinonasal 1 $\alpha$ -Hydroxylase enzyme level in those patients. Sultan et al.,<sup>22</sup> found that Sinonasal epithelial cells produce active vitamin D independently on serum 1,25VD3 by 1- $\alpha$ -hydroxylase. Schlosser et al.,<sup>16</sup> detected that 1 $\alpha$ -Hydroxylase enzyme, in sinonasal mucosa, is decreased in cases of CRSwNP and AFRS. Shahangian et al.,<sup>23</sup> reported that sinonasal epithelial cells possess 1-hydroxylase and are capable of producing 1,25VD3 locally. They came to the conclusion that patients with CRSwNP have decreased antibacterial defences, increased production of inflammatory cytokines, and increased fibroblast proliferation as a result of this molecule's decline.<sup>23</sup> Wang et al.,<sup>24</sup> demonstrated that eotaxin and RANTES production by fibroblasts generated from nasal polyps was significantly increased by IL-1 $\beta$  which is blocked by local vitamin D. Sansoni et al.,<sup>25</sup> discovered that 25-VD3 may be involved in the organisation of RANTES and bFGF production in CRSwNP via controlling the fibroblasts in nasal polyps or other immune cells. Treatment with topical vitamin D supplementation could share in management of CRS with or without polyposis based on the above results. Consequently, Ma et al.,<sup>26</sup> found that topical VD supplementation in CRS patients may be useful in innate epithelial responses. Rostkowska et al.,<sup>27</sup> discovered that as compared to the control group, topical calcitriol or tacalcitol (a VD supplement) therapy reduces IL-6 and IL-8 activation.

#### 4.1. Conclusion

CRS, whether it has polyposis or not, has no correlation with serum vitamin D3 levels. This indicates that low blood levels of 25(OH)D are not likely to be a risk factor for CRS in adult patients, but additional research is required to understand the function of local sinonasal vitamin D3 and its potential application as a topical treatment for those who have CRS, particularly CRSwNP.

#### Conflicts of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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