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ASSOCIATION BETWEEN SERUM VITAMIN D AND CHRONIC RHINOSINUSITIS : A SYSTEMATIC REVIEW

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ABSTRACT

Background: *Chronic rhinosinusitis is a highly heterogeneous chronic inflammation of the upper respiratory tract caused by immune dysfunction in human beings. However, the underlying etiology of this disease has not yet been well established. Several trials have revealed that serum vitamin D level abnormality might play a role in the pathophysiology of chronic rhinosinusitis.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 1.354 articles, whereas the results of our search on SagePub brought up 214 articles. The results of the search conducted for the last year of 2013 yielded a total 4 articles for PubMed and 7 articles for SagePub. In the end, we compiled a total of 6 papers, 4 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria.*

Conclusion: *In summary, our systematic review of 5 studies illustrates the lower serum vitamin D status in CRS patients, which indicates that people might get benefit from appropriate vitamin D supplementation. Therefore, due to the heterogeneity of the subjects, more well-designed prospective RCTs should be carried out to further validate these findings in for the general population in the future.*

Keyword: *Vitamin D, Chronic Rhinosinusitis*

INTRODUCTION

Chronic rhinosinusitis (CRS) is a disease of the nasal and paranasal mucosa characterized by the persistent inflammation with distinctive inflammatory cells. Epidemiologic studies have revealed wide variation in the prevalence of CRS among regions globally. According to the data of 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS2012), the overall prevalence of CRS is 5%–15% in Western populations. In addition, CRS is ranked as one of the top 10 costly healthy conditions to US employers, overcoming asthma costs. Thus, we believe that CRS is still an undervalued disease and represents a large socioeconomic burden.[1]

Chronic rhinosinusitis (CRS) encompasses a broad group of disorders characterized by persistent inflammation of the nasal mucosa and paranasal sinuses that affects up to 16% of the US population and creates a significant socio-economic burden. While the immunopathogenesis of CRS remains largely unknown, current research has provided better insight into potential etiologies. The current evidence supports two predominant immune phenotypes in CRS that arise secondary to skewing of the T helper (Th) cells. In general, CRS without nasal polyposis (CRSsNP) is Th1-skewed whereas CRS with nasal polyposis (CRSwNP) is Th2-skewed. This skewing impacts expression of local inflammatory mediators, which subsequently act in an autocrine and paracrine fashion to influence the local mucosal inflammatory response that is characteristic of CRS. The mechanism of T cell differentiation is incompletely understood, but is likely regulated by the complex interplay of the local cytokine milieu, activation signals and the inflammatory cell infiltrate. The local inflammatory mediator profile for CRS subtypes is still under investigation, but evidence suggests that CRSsNP and CRSwNP are unique disease entities associated with separate and distinct inflammatory mediator profiles within the sinonasal mucosa or mucus. Additionally, these differing mediator profiles may explain the disparate histologic findings and distinct inflammatory cell profiles seen in CRS subtypes[2].

The specific pathogenesis of CRS isn't totally clear. In the past, CRS was considered to be a chronic suppurative inflammation caused by bacterial infection. At present, more and more studies have demonstrated that CRS is a highly heterogeneous chronic inflammation of the upper respiratory tract caused by immune dysfunction in human beings. Based on the radiologic and endoscopic findings, CRS could be divided into two distinct clinical phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). The immunologic mechanism of these two phenotypes is different. Briefly, CRSwNP is characterized as an end product of Th2 cell skewing, mediated by IL-4, IL-5, IL-13. In contrast, CRSsNP is typically considered a result of a Th1 inflammation via, with dominant production of IFN-γ.[3]

It is generally considered that vitamin D could maintain the healthy balance of calcium and phosphorus playing an important role in the bone metabolism. Increasing number of studies have revealed that vitamin D has a wide range of biological functions, not only in the calcium and phosphorus metabolism, but also in hormone secretion, cell proliferation and differentiation. As an immune-modulatory steroid hormone, Vitamin D3 (VD3) directly regulates a variety of cell types, including monocytes, macrophages, epithelial cells, dendritic cells and T-cells. Through blocking monocyte to DC differentiation and maturation and thus diminishing DCs stimulation of T cell Th1/Th2 differentiation, vitamin D influences the process of immune response. Although the exact mechanisms remain unclear, recent evidences support that vitamin D might play an important role in the pathophysiology of CRS. Serum 25-Hydroxyvitamin D (25(OH)D) levels are considered the chief circulation forms of vitamin D and are representative of body vitamin D status. Besides, some authors point out that VD3 seemed more appropriate than vitamin D2 to sustain adequate levels of 25(OH)D and that vitamin D deficiency was associated with CRSwNP.[4,5]

To the best of our knowledge, no systematic evaluation have been conducted on the relationship between serum vitamin D levels and CRS or healthy controls.

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we review published literature of vitamin D in chronic rhinosinusitis. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "vitamin D" and "chronic rhinosinusitis" as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *(("vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]) AND ("rhinosinusal"[All Fields] OR "rhinosinusitis"[All Fields])) AND ((clinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) AND (2013:2023[pdat]))* used in searching the literature.

Data retrieval

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.

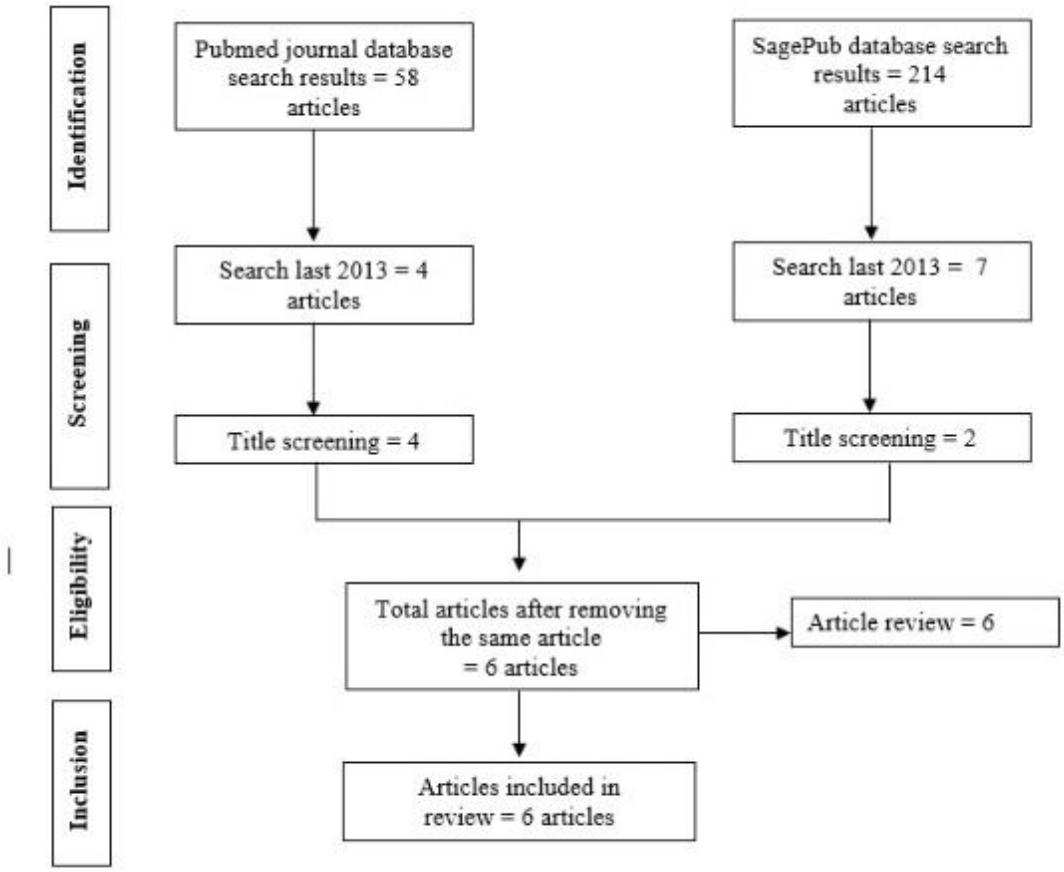

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 1.354 articles, whereas the results of our search on SagePub brought up 214 articles. The results of the search conducted for the last year of 2013 yielded a total 4 articles for PubMed and 7 articles for SagePub. In the end, we compiled a total of 6 papers, 4 of which came from PubMed and 2 of which came from SagePub. We included five research that met the criteria.

Yenigun, et al[6] (2015) showed that found the lower plasma vitamin D levels in patients with rhinosinusitis when comparerd with the control group.

Mostafa, et al[4] (2016) showed that 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.

Baruah, et al[7] (2020) showed that a greater VD deficiency in CRS patients was revealed. The authors continued their study and separated the VD-deficient sample suffering from CRS into two subgroups. One subgroup received oral VD supplementation, and the other received a placebo. It was therefore shown that the additional administration of VD contributed to the relief of their symptoms.

Table 1. The litelature include in this study

Author	Origin	Method	Sample	Result
Yenigun et al, 2015[6]	USA	Observational studies	42 patients	Group one included 42 ARC patients (15 male, 27 female, ages between 12 and 43, average age 25.7 ∓ 8.6); group two included 35 healthy people (15 male, 200female, ages between 12 and 44, average age 26.9 ∓ 9.1). Plasma 25-hydroxyvitamin D levels of the subjects with ARC group (7.33 ∓ 3.61 ng/mL, standard error mean: 0.55, range 3.17–13.68 ng/mL) were significantly lower than the control group (13.37 ∓ 5.42 ng/mL, standard error mean: 0.91, range 6.84–25.92 ng/mL) (p = 0.010, Independent-Samples test).
Mostafa et al, 2016[4]	Egypt	Prospective case control studies	74 patients	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 ($p = 0.001$).
Baruah et al, 2020[7]	India	Retrospective 1 year studies	200 patients	Of the 200 subjects with CRS, 100 were given oral vitamin D supplementation in the form of Cholecalciferol 60000IU weekly once for 3 months and the other group were treated with placebo. Before the treatment, the average level of serum Vitamin D was 12.31 ng/ml. After 3 months, it increased significantly to 29.71 ng/ml. Similarly, the pretreatment TNSS score was on average 11.92. After 3 months, the scores fell by an average of 10.65 points, a significant statistical difference ($P < 0.05$).
Tomaszewska et al, 2019[8]	USA	Retrospective studies	52 patients	The studied group comprised 52 patients with CRS without nasal polyps (sNP), 55 with CRS with nasal polyps (wNP), and 59 in the control group. The endpoints were determined by appropriate methods. We conducted immunohistochemical staining of gathered tissue from the ostiomeatal complex for determination of VDR and 1α-hydroxylase. Analytical results were compared with clinical data as already noted. A decrease in VDR nuclear staining occurred in CRS patients as compared to controls. Insignifcant differences were observed in 1α-hydroxylase, expression in all studied groups, while VDR and cytochrome CYP27B1 protein expression (1α-hydroxylase) correlated with clinical data.
Thakur et al, 2021[9]	India	Prospective case control studies	60 patients	A significantly lower vitamin D levels were found in CRS (14.60 ± 7.68 ng/ml), CRSwNP (13.70 ± 7.88 ng/ml) and CRSsNP (15.49 ± 7.50 ng/ml), when compared to controls (29.36 ± 7.49 ng/ml). Non allergic cases when compared with controls, showed significantly lower vitamin D levels (13.91 ± 6.78 compared to 29.36 ± 7.49

				ng/ml). LMS and LKS in CRS showed a moderate correlation with vitamin D (r_s: - 0.604 for LMS, r_s: - 0.595 for LKS). Logistic regression analysis showed vitamin D levels (Odds-Ratio 0.783) to be an independent predictive factor of CRS.
Zand et al, 2020[10]	Iran	Cross sectional studies	93 patients	The mean age and serum vitamin D level of the patients were measured at 37.7±13.6 years and 24.6±16.9 ng/ml, respectively. Moreover, the mean of LMS and SNOT-22 scores were calculated at 14.2±11.2 and 40.8±17.6, respectively. There was a negative correlation between the SNOT-22 and serum levels of vitamin D (P=0.034). Similarly, LMS and serum vitamin D levels were correlated negatively (P=0.027). Furthermore, the results revealed a direct relationship between LMS and SNOT-22 (P<0.0001).

Tomaszewska, et al[8] (2019) showed that a decrease in VDR nuclear staining occurred in CRS patients as compared to controls. Insignificant differences were observed in 1α-hydroxylase, expression in all studied groups, while VDR and cytochrome CYP27B1 protein expression (1α-hydroxylase) correlated with clinical data. They divided into three groups: CRSwNP, CRSsNP, and healthy individuals, and tissue from the middle nasal duct complex was also obtained to determine the levels of VDR and 1-α hydroxylase. A reduction in VDRs was found in CRS patients compared to healthy controls. Insignificant differences were observed in the expression of 1-α hydroxylase in the studied groups. Thus, it appeared that perhaps VD, its receptors, and its enzymes play an important role in CRS.

Thakur, et al[9] (2021) showed that a significantly lower vitamin D level is associated with CRS, irrespective of presence or absence of nasal polyposis in adults residing at high altitudes. Vitamin D is an independent predictive factor for CRS. There is an inverse moderate correlation of severity of CRS with vitamin D.

Zand, et al[10] (2020) showed that according to the obtained results, there was a significant relationship between the serum vitamin D levels and severity of disease in patients with CRS w NP. Therefore, serum vitamin D levels could be added to the routine workup of the patients suffering from CRS w NP.

DISCUSSION

Rhino sinusitis is a group of diseases associated with the inflammation of the nasal mucosa and paranasal sinuses. When the symptoms last for at least 12 consecutive weeks, it is called chronic rhino sinusitis (CRS). TheCRS can be associated with nasal polyposis (CRSwNP) or without nasal polyposis (CRSsNP). The CRSsNP is a persistent inflammation resulting from the lack of the complete remission of acute infectious rhino sinusitis. On the other hand, CRSwNP is a disorder with various causes and pathogenesis, including fungi, resistant bacteria, super antigens, biofilms, mucosal disorders, environmental stimuli, sinonasal obstructions (especially osteomeatal complexes), and osteitises.[10]

Vitamin D deficiency is related to atopic diseases, such as asthma, allergic rhinitis, and anaphylaxis. In addition, it is known that it has a deleterious effect on the musculoskeletal system. Currently, many physicians measure the level of vitamin D as part of a preliminary laboratory test. From the immunological viewpoint, CRS w NP results from T helper II activity, while CRSsNP is a T helper type I driven inflammation. Some signs and symptoms of CRSwNP result from type 2 immune response to a variety of stimulants.[10]

Playing an essential role in anti-inflammation and anti-proliferation, vitamin D is known as an immunomodulator. After initial hydroxylation in liver, vitamin D transforms to the prohormone calcidiol (25(OH)D3), which would circulate and active to calcitriol (1.25(OH)D3) by 1-α-hydroxylase in peripheral tissues. After binding to the intracellular Vitamin D

Receptor (VDR), a number of cell signaling pathways are activated. In vitro studies have shown that 1.25(OH)D3 could reduce the expression of pro-inflammatory cytokines (IL-6, IL-8, RANTES, eotaxin) by human sinonasal epithelial cells. Furthermore, vitamin D is necessary for T-regulatory cell activity and T-cell responses to infection. Through these features mentioned above, vitamin D was considered to be one of the important factors that could influence the pathogenesis of CRS.[11]

VD deficiency is a worldwide public health issue. Obesity, lack of physical activity, and less time outdoors negatively affect its levels. It is known that origin and climate peculiarities affect VD levels. VD levels are typically higher in countries with more sunny days, although lifestyle modifications can mitigate this effect. Physical mechanisms such as angiogenesis, mucositis, and proliferation are closely connected with CRS, a malfunction due to low serum VD levels.[11] VD has anti-inflammatory actions, inhibits inflammatory cell proliferation, and acts as an immunomodulator agent. After initial hydroxylation in the liver, VD is transformed into the prohormone calcidiol (25(OH)D3), which is converted to calcitriol (1,25(OH)D3) by 1-α-hydroxylase mainly in the kidneys and other distal tissues. Then, it binds to the VD receptor in the cells (VDR), and many cell signaling pathways are activated. Expression of proinflammatory cytokines (IL-6, IL-8, RANTES, and eotaxin) could be reduced in human nasal epithelial cells by 1,25(OH)VD, as shown in in vitro studies. In addition, VD is essential for T-cell responses and T-regulatory cell responses to inflammation. Based on the above-mentioned evidence, VD significantly influences the pathogenesis of CRS in combination with other agents. Due to the conflicting conclusions among existing studies, there is controversy concerning the relationship between VD levels and CRS, and till now, no consensus exists. To resolve this issue, well-designed and randomized controlled trials are paramount to establishing evidence-based medicine. More specifically, in the epidemiological study of a large sample by Lee et al. published in 2018, a significant contrast to the previously published studies was revealed, as the authors concluded that serum 25OH VD levels were higher in adult patients with CRS than those without CRS in South Korea. This epidemiological study contrasts with the majority of the current evidence concerning the relationship between VD levels and CRS and highlights that VD deficiency does not constitute a risk factor for CRS development. It is worth noting that this is the only large study, which is contrary to the current evidence.[12]
The prevalence of CRS is high, but its therapy is complicated in many cases because of the involvement of a variety of mechanisms in the etiology of the disease. Presently, treatment of CRS relies on nasal glucocorticoid sprays in combination with saline (>200 mL). Mucosal eosinophilia predisposes to CRS relapse, and current literature confirms the relationship between mucosal eosinophilia and postoperative recurrence. It seems that eosinophils are useful biomarkers for CRS severity, possibly resulting immediately in the genesis of CRSwNP with T-helper type 2 (Th2) inflammation. However, the current therapy with biological factors is successful in 50% of the patients.[13]

Vitamin D can inhibit the synthesis and release of interleukin 4 (IL-4) andIL-10. The IL-4 and IL-10 are the most prominent cytokines in type 2 immune response, which provoke synthesis and secretion of interferon gamma, as the most important cytokine in type 1 immune response. Moreover, vitamin D may contribute to the effects of glucocorticoid on cells, and higher doses of glucocorticoids are needed in vitamin D deficiency states to achieve therapeutic effects. Recently, Vitamin D gained attention in medical research and its role in the pathophysiology of several chronic diseases has been investigated. Since CRS is associated with asthma and atopy, it can be assumed that vitamin D in CRS plays a similar role to that in asthma and atopy. With this background in mind, the current study was conducted to investigate the association between serum vitamin D levels and severity of disease in CRS patients.[10]

CONCLUSION

In summary, our systematic review of 5 studies illustrates the lower serum vitamin D status in CRS patients, which indicates that people might get benefit from appropriate vitamin D supplementation. Therefore, due to the heterogeneity of the subjects, more well-designed prospective RCTs should be carried out to further validate these findings in for the general population in the future.

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