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Association of Vitamin D Status and Acute Rhinosinusitis

Results From the United States National Health and Nutrition Examination Survey 2001–2006

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Abstract: Although vitamin D status may be a modifiable risk factor for various respiratory ailments, limited data exists regarding its role in sinonasal infections. Our goal was to investigate the association of 25-hydroxyvitamin D (25OHD) levels with acute rhinosinusitis (ARS) in a large, nationally representative sample of non-institutionalized individuals from the United States.

In this cross-sectional study of individuals ≥17 years from the National Health and Nutrition Examination Survey 2001–2006, we used multivariable regression analysis to investigate the association of 25OHD levels with ARS, while adjusting for season, demographics (age, sex, race, and poverty-to-income ratio), and clinical data (smoking, asthma, chronic obstructive pulmonary disease, diabetes mellitus, and neutropenia).

A total of 3921 individuals were included in our analyses. Median 25OHD level was 22 (interquartile range 16–28) ng/mL. Overall, 15.8% (95% confidence interval [CI] 14.4–17.7) of participants reported ARS within the 24 hours leading up to their survey participation. After adjusting for season, demographics, and clinical data, 25OHD levels were associated with ARS (odds ratio 0.88, 95% CI 0.78–0.99 per 10 ng/mL). When vitamin D status was dichotomized, 25OHD levels <20 ng/mL were associated with 33% higher odds of ARS (odds ratio 1.33, 95% CI 1.03–1.72) compared with levels ≥20 ng/mL.

Our analyses suggest that 25OHD levels are inversely associated with ARS. Randomized, controlled trials are warranted to determine the effect of optimizing vitamin D status on the risk of sinonasal infections.

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Abbreviations: 25OHD = 25-hydroxyvitamin D, ARS = acute rhinosinusitis, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CRS = chronic rhinosinusitis, DM = diabetes mellitus, FPL = federal poverty limit, NHANES = National Health and Nutrition Examination Survey, OR = odds ratio.

INTRODUCTION

Acute rhinosinusitis (ARS) affects >30 million Americans every year and accounts for roughly 16 million annual office visits.[1,2] ARS is associated with significant morbidity and lost time from work.[3,4] Indeed, the socioeconomic impact of ARS likely exceeds $6 billion annually.[5] Despite the fact that >98% of cases are due to viral infections associated with the common cold,[6] ARS remains the fifth leading cause of antibiotic prescription in the United States.[1,7] Recognizing that such practices facilitate antimicrobial resistance,[8] consensus statements have emphasized the avoidance of antibiotics for the vast majority of patients with ARS.[9–12] Although well-defined treatment guidelines exist for managing ARS,[1,12,13] evidence-based preventative strategies are limited.

The initial step in the pathogenesis of ARS is mucosal inflammation, which leads to ciliary dysfunction and ostial obstruction.[14] This creates a stagnant pool of secretions within the sinonasal cavities that is ideal for viral, bacterial, and/or fungal growth. Recent evidence suggests that vitamin D promotes anti-inflammatory effects in human sinonasal epithelial cells,[15] and it is also a potent regulator of the innate and adaptive immune systems.[16] Moreover, although it has been proposed as a potentially modifiable risk factor for various respiratory infections,[17,18] the relationship between vitamin D status and ARS has not been previously explored. Therefore, our goal was to investigate the association of serum 25-hydroxyvitamin D (25OHD) levels (the most widely recognized indicator of total body vitamin D status) with ARS in a large, nationally representative sample of noninstitutionalized individuals from the United States.

METHODS

Source Data

The National Health and Nutrition Examination Survey (NHANES) data are nationally representative, cross-sectional samples of the noninstitutionalized, civilian population of the United States.[19] They have been used extensively to report on the association of various biomarkers with major diseases. Conducted by the National Center for Health Statistics (Atlanta, GA), and after 3 large phases between 1971 and 1994, the survey was converted into an annual process between 1999 and

2010. The most recent surveys with 25OHD assessment were between 2001 and 2002, 2003 and 2004, and 2005 and 2006. During this period, 31,509 individuals were interviewed, and 30,070 individuals completed physical examinations and laboratory testing. In addition, to allow for better population estimates, there was oversampling of individuals from the following categories: age 12–19 years, age ≥70 years, non-Hispanic black, Mexican American, and low-income white. We conducted a secondary analysis of this large dataset (NHANES 2001–2006), after the Partners Human Research Committee (local institutional review board) granted an ''exempt'' status for the study.

Data Collection

Detailed survey methods, including sampling, interview, examination, laboratory measurements, ethics approval, and informed consent have previously been reported.[20] In summary, the survey used a complex, stratified, multistage probability sample design to recruit nationally representative samples. Approximately 12,000 individuals were invited to participate in each 2-year NHANES cycle. The surveys were performed during scheduled in-home interviews to obtain demographic information, as well as data on health and nutrition. Physical examinations and laboratory testing were performed in either a mobile examination center or during a home visit. Blood samples collected during the examination were centrifuged, aliquoted, and stored at −70°C on-site. They were then shipped on dry ice to central laboratories, where they were stored at −70°C until analysis. Serum 25OHD levels were measured using a radioimmunoassay kit after extraction with acetonitrile (DiaSorin, Stillwater, MN) by the National Center for Environmental Health (Atlanta, GA). NHANES modified the 2003–2006 values for 25OHD in November 2010 to address observed drifts in assay performance following reagent and calibration lot fluctuation.[20]

Data Abstraction

We limited our analysis to the 3921 individuals, ≥17 years, with reported serum 25OHD levels (primary exposure) and who answered the survey question: ''Have you had a cold, sinus problem, or earache in the last 24 hours?'' (primary outcome). To most accurately adjust for the effect of season on 25OHD levels, we recorded the 6-month block within which the laboratory samples were collected. We also abstracted information on all participants in the NHANES 2001–2006 datasets related to age, sex, race, poverty-to-income ratio, and season. We also abstracted smoking status and several self-reported current diseases including, asthma, chronic obstructive pulmonary disease (COPD), and diabetes mellitus. A diagnosis of COPD was based on responses to questions on emphysema and/or chronic bronchitis. We attempted to control for a history of allergic rhinitis; however, the number of missing data points was too large to include it in our regression analysis. Moreover, finally, we used laboratory data to document cases of neutropenia.

Statistical Analysis

All statistical analyses were performed using Stata 12 (StataCorp LP, College Station, TX). Using survey commands, we applied the recommended subsample weights for the interview plus examination data to account for unequal probabilities of selection and to accurately represent estimates for the population of the United States. All of the results are presented as weighted values. We calculated the variance based on NHANES-provided masked variance units using the Taylor series linearization method. All of the reported P values are 2-tailed, with $P < 0.05$ considered statistically significant. We calculated proportions with 95% confidence intervals (CIs) for demographic features and other factors thought to be related to ARS, overall and in the subset of participants with self-reported ARS, within 24 hours of the interview.

To graphically represent the unadjusted relationship between 25OHD levels and ARS, we constructed a cumulative frequency curve using locally weighted scatter plot smoothing (LOWESS). LOWESS is a type of nonparametric regression, which summarizes the relationship between 2 variables in a fashion that initially relies on limited assumptions about the form or strength of the relationship.[21] The rationale and methods underlying the use of LOWESS for depicting the local relationship between measurements of interest across parts of their ranges are available elsewhere.[22]

For our primary analysis, we first considered serum 25OHD level as a continuous variable and then as a dichotomous variable based on clinically relevant threshold levels.[23] To improve interpretability of the analysis, we also dichotomized some of the variables as follows: season (May 1 to October 31 as high-ambient ultraviolet B radiation vs November 1 to April 30 as low-ambient ultraviolet B radiation), race (nonwhite versus white), poverty-to-income ratio (≤federal poverty level vs >federal poverty level), and neutropenia (white blood cell count $<3.5 \times 10^9$/L vs $\geq 3.5 \times 10^9$/L). We further dichotomized self-reported histories of smoking, asthma, COPD, and diabetes mellitus. We determined unadjusted associations between risk factors and the outcome of ARS using the Pearson χ^2 test for categorical variables and simple ordinal logistic regression for ordinal variables. To evaluate the independent association between serum 25OHD level and ARS, we created multivariable models by progressively adding covariates that might confound or alter the association of 25OHD with ARS. All adjusted odds ratios (ORs) for the variables in the models are reported with 95% CIs.

We performed an a priori sample size calculation to ensure that the study would be able to detect meaningful differences between 25OHD levels and the risk of ARS. From existing data, we assumed that the point prevalence of ARS in the general population was 14%.[3] Based on conservative estimates regarding clinically meaningful thresholds for vitamin D status,[23] we considered patients as having 25OHD levels <20 versus ≥20 ng/mL. We also assumed that a minimum clinically meaningful difference in absolute risk of ARS between groups was 30%. Based on these assumptions, we expected the prevalence of ARS in participants with 25OHD <20 ng/mL to be 16% and in those with levels ≥20 ng/mL to be 12%. With α set at 0.05, 1181 individuals would be required in each group to detect this difference with a power of 80%.

RESULTS

Characteristics of the analytic cohort are given in Table 1. The median age of the participants was 47 (IRQ 33–63) years; 51% were women and 54% were white. Overall, the median serum 25OHD level was 22 (IRQ 16–28) ng/mL; 7.1% of the participants had 25OHD levels 0–9.9 ng/mL, whereas 33.7% had levels 10–19.9 ng/mL and 40% had levels 20–29.9 ng/mL. Overall, 15.8% (95% CI 14.4–17.7) of participants reported ARS within the 24 hours leading up to their NHANES interview. The proportion of participants with recent ARS, stratified by individual characteristics, is also presented in Table 1.

LOWESS analysis showed a near-linear relationship between 25OHD level and the cumulative frequency of ARS

TABLE 1. Overall Sample Characteristics and Subgroups With ARS Infections

	Total	ARS Infection (Row %)	*P*
Age			
17–39 y	1451	205 (14.2)	0.10
40–60 y	1227	204 (16.6)	
≥60 y	1243	210 (16.9)	
Sex			
Female	2019	366 (18.1)	**<0.001**
Male	1902	254 (13.4)	
Race			
White	2119	353 (16.7)	0.12
Nonwhite	1802	267 (14.8)	
Poverty-to-income ratio			
≤FPL	696	113 (16.2)	0.74
>FPL	3225	507 (15.7)	
Season			
High ambient ultraviolet B radiation	2157	299 (13.8)	**<0.001**
Low ambient ultraviolet B radiation	1764	321 (18.2)	
25OHD			
<20 ng/mL	1765	305 (17.3)	**0.02**
≥20 ng/mL	2156	315 (14.6)	
Smoking			
No	1959	293 (15.0)	0.14
Yes	1962	327 (16.7)	
Asthma			
No	3456	529 (15.3)	**0.02**
Yes	465	91 (19.6)	
COPD			
No	3758	568 (15.1)	**<0.001**
Yes	163	52 (31.9)	
Diabetes mellitus			
No	3504	545 (15.5)	0.20
Yes	417	75 (18.0)	
Neutropenia			
WBC $< 3.5 \times 10^9$/L	33	5 (13.2)	0.65
WBC $\geq 3.5 \times 10^9$/L	3883	615 (15.8)	

Statistically significant *P* values are shown in bold. 25OHD = 25-hydroxyvitamin D, ARS = acute rhinosinusitis, COPD = chronic obstructive pulmonary disease, FPL = federal poverty limit, WBC = white blood cell.

up to 25OHD levels ~30 ng/mL (Figure 1). Between 25OHD levels of 30 and 60 ng/mL, there was an increasing flattening of the curve. Beyond 60 ng/mL, the curve remained flat (ie, there were no additional cases of ARS).

When 25OHD was treated as a continuous variable, there was an inverse relationship between vitamin D status and ARS (OR 0.88, 95% CI 0.78–0.99 per 10 ng/mL). Compared with individuals with 25OHD levels ≥20 ng/mL, those with levels <20 ng/mL had a 33% higher adjusted odds of ARS (OR 1.33, 95% CI 1.03–1.72) within 24 hours of the interview. Other characteristics associated with increased risk of ARS in these models were race, sex, history of COPD, and season (Table 2). On the contrary, compared with individuals with 25OHD levels ≥30 ng/mL, those with levels <30 ng/mL had an 18% higher adjusted odds of ARS (OR 1.18, 95% CI 0.93–1.49) within 24 hours of the interview.

DISCUSSION

In this large, nationally representative sample of noninstitutionalized individuals in the United States, we investigated whether 25OHD levels were associated with ARS and demonstrated that vitamin D status is inversely associated with ARS. This relationship was most pronounced when comparing individuals with 25OHD levels <20 ng/mL to those with levels ≥20 ng/mL. Although previous studies have shown that vitamin D status is associated with the risk of various respiratory diseases,[24–28] our work provides important supporting evidence to suggest that appropriate vitamin D supplementation may offer a novel approach to lowering the risk of ARS and by extension the risk of chronic rhinosinusitis (CRS) in the general population.

Although the observational, cross-sectional design of the present study limits any causal inference about the effect of low 25OHD levels and higher risk of ARS, the biological plausibility is undeniable. In vitro studies have shown that exogenous 1,25-dihydroxyvitamin D, the most biologically active vitamin D metabolite, attenuates the expression of proinflammatory cytokines (interleukin-6, interleukin-8, and chemokine ligand 20) by human sinonasal epithelial cells after exposure to cigarette smoke.[16] Therefore, low systemic 25OHD levels may interfere with natural mechanisms to limit the mucosal

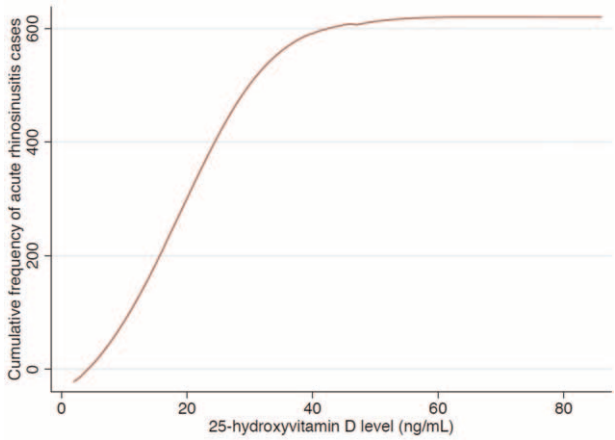

FIGURE 1. Near-linear relationship of the cumulative frequency in acute rhinosinusitis cases and 25OHD levels up to 30 ng/mL in LOWESS analysis. Between 25OHD levels of 30 and 60 ng/mL, there was flattening of the curve, and beyond 60 ng/mL the curve remained flat (no additional cases of ARS). 25OHD = 25-hydroxyvitamin D, ARS = acute rhinosinusitis, LOWESS = locally weighted scatterplot smoothing.

inflammation that precipitates an episode of ARS. Moreover, cells of the innate and adaptive immune system express the vitamin D receptor,[29] and, in low vitamin D states, dysfunctional macrophage activity becomes evident.[30] Vitamin D is necessary for T-cell responses to infection,[31] and it is also an important link between Toll-like receptor activation and antibacterial responses.[32] Macrophages stimulated by Toll-like receptors induce further vitamin D receptor expression[33] and conversion of 25OHD to 1,25-dihdroxyvitamin D.[34] This, in turn, leads to increased production of cathelicidin, an endogenous antimicrobial peptide with potent activity against bacteria, viruses, fungi, and mycobacteria.[35–37] Cathelicidin is also highly expressed by epithelial cells at natural barrier sites (eg, skin, gut, and lungs) and may represent an important first line of defense for the innate immune system[38] against pathogens. Indeed, human sinonasal cells have been shown to express cathelicidin[39] and upregulate production of the antimicrobial peptide when exposed to gram-positive and gram-negative bacteria.[40] Therefore, the suboptimal expression of cathelicidin in the setting of low systemic 25OHD levels is another potential mechanism by which low vitamin D status may increase the risk of ARS.

TABLE 2. Multivariable Model With ORs and 95% CIs for the Association of 25OHD Level and ARS

Variable	OR (95% CI)
Age	1.00 (1.00–1.01)
Sex (female vs male)	**1.30 (1.05–1.61)**
Race (white vs nonwhite)	**1.39 (1.05–1.82)**
Poverty-to-income ratio (≤FPL vs >FPL)	1.09 (0.83–1.43)
Season (low vs high ambient radiation)	**1.35 (1.04–1.74)**
25OHD (<20 ng/mL vs ≥20 ng/mL)	**1.33 (1.03–1.72)**
Smoking	1.19 (0.98–1.46)
Asthma	1.02 (0.77–1.35
COPD	**2.04 (1.37–3.01)**
Diabetes mellitus	1.01 (0.73–1.39)
Neutropenia	1.04 (0.33–3.23)

Statistically significant ORs are shown in bold. 25OHD = 25-hydroxyvitamin D, ARS = acute rhinosinusitis, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FPL = federal poverty limit, OR = odds ratio.

ARS is a major risk factor for chronic infections of the sinonasal cavity. Moreover, although our findings are novel, previous studies have investigated the role of vitamin D status in CRS. Indeed, reports suggest that low 25OHD levels are prevalent in patients with CRS, especially in nonwhite individuals[41–43] and in those with allergic fungal rhinosinusitis[44] or those with nasal polyps (chronic rhinosinusitis with polyps).[43] At a mechanistic level, in patients with allergic fungal rhinosinusitis or chronic rhinosinusitis with polyps, vitamin D status has been shown to be inversely associated with systemic expression of mature dendritic cells, regulated upon activation of normal T cells expressed and secreted, and basic fibroblast growth factor.[44–46] Moreover, low 25OHD levels are associated with greater sinonasal bone erosion,[44] and cholecalciferol (vitamin D3) has been shown to improve bone metabolism in the paranasal sinuses.[47] Moreover, although these studies provide intriguing preliminary data, they also underscore the need for adequately powered, well-designed, randomized, placebo-controlled trials to determine whether vitamin D may be beneficial for the prevention of sinonasal disease in the general population.

Although our results provide compelling evidence to suggest that vitamin D status may be a modifiable risk factor for ARS in the general population, it is important to discuss the potential limitations of the present study. As with all observational studies, and any cross-sectional research design, there is potential for confounding due to the lack of a randomly distributed exposure. Indeed, we were unable to control for a history of allergic rhinitis and nasal polyps, which are known risk factors for sinonasal infections. Moreover, despite adjusting for multiple other potential confounders, there may still be residual confounding, which could account for the observed differences in outcomes. In particular, low 25OHD levels may be a reflection of poor general health or suboptimal nutritional state, for which we are unable to fully adjust. We are also unable to fully adjust for lack of sun exposure, use of sunscreens, physical activity, and vaccination status. Given the confines of the NHANES 2001–2006 survey, a further limitation is that we were unable to control for ARS exclusively because the survey question also asked about ''colds'' and ''earaches.'' However, isolated otitis media is extremely rare in adults, and colds are highly associated with acute sinonasal infections.[48] As such, the analytic cohort was likely composed of an overwhelming majority of individuals with the exposure of interest. It is also important to note that when 25OHD levels were dichotomized as <30 versus ≥30 ng/mL, our multivariable regression analysis did not demonstrate a statistically significant association of vitamin D status with ARS; our study was underpowered to detect differences at this threshold level because only 652 (17%) participants in the analytic cohort had 25OHD levels ≥30 ng/mL. Moreover, finally, the NHANES dataset relies on a self-reported history of ARS, which may be prone to recall bias. These and other potential issues will need to be addressed in future studies to replicate and extend our findings.

CONCLUSIONS

In summary, these data demonstrate that low 25OHD levels are strongly associated with ARS in a large, nationally

representative sample of noninstitutionalized individuals from the United States. Longitudinal studies are required to confirm our findings and establish the mechanisms underlying these observations. Moreover, high-quality, randomized controlled trials are warranted to determine whether vitamin D supplementation in individuals with low vitamin D status may affect the incidence and severity of ARS in the general population.

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