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ORIGINAL RESEARCH

Correlation Between Subepithelial Fibrosis and Vitamin D Deficiency in Chronic Rhinosinusitis with Nasal Polyps: Insights from Histological and Transcriptomic Analyses

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Purpose: To investigate the correlation between serum vitamin D status and clinical, histological, and gene expression profiles in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

Patients and Methods: This observational study enrolled patients with CRSwNP from November 2019 to September 2021, and diagnoses were confirmed according to the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020). Clinical features, histopathological characteristics, and gene expression profiles were analyzed across groups with serum vitamin D deficiency status. Histopathological evaluations and mRNA sequencing were performed on a subset of nasal polyp specimens.

Results: Among 101 patients with CRSwNP, a comprehensive analysis revealed no significant correlation between vitamin D deficiency and most clinical parameters or treatment prognosis, except for a notable age difference among groups with serum vitamin D-deficiency, insufficiency, and sufficiency. Histologically, a higher prevalence of subepithelial fibrosis was observed in the vitamin D-deficient group. Moreover, transcriptomic analysis demonstrated significant differences in expression profiles among the groups, with upregulated genes in the deficient group enriched in extracellular matrix components and downregulated genes related to axoneme assembly and cilium movement.

Conclusion: Our findings suggest a connection between vitamin D deficiency and subepithelial fibrosis in nasal polyps, pointing to a possible involvement of vitamin D status in fibrosis-related pathological processes in CRSwNP.

Keywords: chronic rhinosinusitis, nasal polyps, vitamin D deficiency, tissue fibrosis, transcriptomic profiles

Introduction

Chronic rhinosinusitis (CRS) represents an inflammatory disorder affecting 8–14% of the global population.[1,2] CRS is commonly classified into two phenotypes: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) based on polyp presence. The increasing interest in CRSwNP research is attributed to its complex pathogenesis, significant symptom burden, and challenging management.[3,4] In Western countries, CRSwNP predominantly exhibits a Type 2 (T2) inflammation pattern.[5] In contrast, patients from China demonstrate a mixed Type 1 (T1) and Type 3 (T3) inflammatory profile,[6] underscoring the heterogeneity in inflammatory mechanisms and downstream tissue remodeling processes across different populations.

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Vitamin D, a steroid hormone, undergoes an initial hepatic hydroxylation to form the circulating metabolite 25-hydroxyvitamin D (25(OH)D), which is subsequently converted into its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), primarily through renal hydroxylation. Serum 25(OH)D status is influenced by environmental and regional factors, for example, sunlight exposure, season, and latitude. Vitamin D is recognized for its immunomodulatory properties,[7–9] including the differentiation of Th17 cells,[10] proliferation of activated B cells, and generation of plasma cells.[11] Recent investigations have also highlighted vitamin D's role in modulating neutrophilic and eosinophilic inflammation.[9,12] Although the precise role of vitamin D in CRSwNP pathogenesis is still being elucidated, accumulating evidence points towards a significant involvement in its pathophysiology.

Furthermore, serum levels of 25(OH)D may serve as a potential independent predictor for chronic diseases, with accumulating evidence linking vitamin D deficiency to CRSwNP.[13] However, a key unresolved question is whether vitamin D influences the structural pathology of CRSwNP, particularly tissue remodeling and fibrosis. Previous in vitro work suggests that vitamin D can inhibit fibroblast proliferation and suppress matrix metalloproteinase expression, indicating potential effects on tissue remodeling in CRSwNP.[14] However, the in vivo relationship and functional significance of vitamin D with respect to the pathological structural characteristics of nasal polyps are still unclear.

This study compared clinical and histological features among CRSwNP patients stratified by serum vitamin D status (deficient, insufficient, and sufficient). Additionally, we investigate gene expression profiles between CRSwNP patients with and without serum vitamin D deficiency. Collectively, our research aims to delineate vitamin D–associated characteristics of CRSwNP and to explore molecular pathways potentially involved in fibrosis-related structural remodeling of nasal polyps.

Materials and Methods

Cohort

This was a single-center, retrospective study. We enrolled consecutive patients admitted to the Department of Otorhinolaryngology, Seventh Affiliated Hospital of Sun Yat-sen University, between November 2019 and September 2021. During the study period, 126 patients with CRSwNP were initially screened. A study flowchart illustrating the patient selection process is presented in Figure 1. Eligible participants were individuals aged 16 years or older who were scheduled to undergo bilateral endoscopic sinus surgery (ESS) for CRSwNP. The diagnosis for CRSwNP was independently

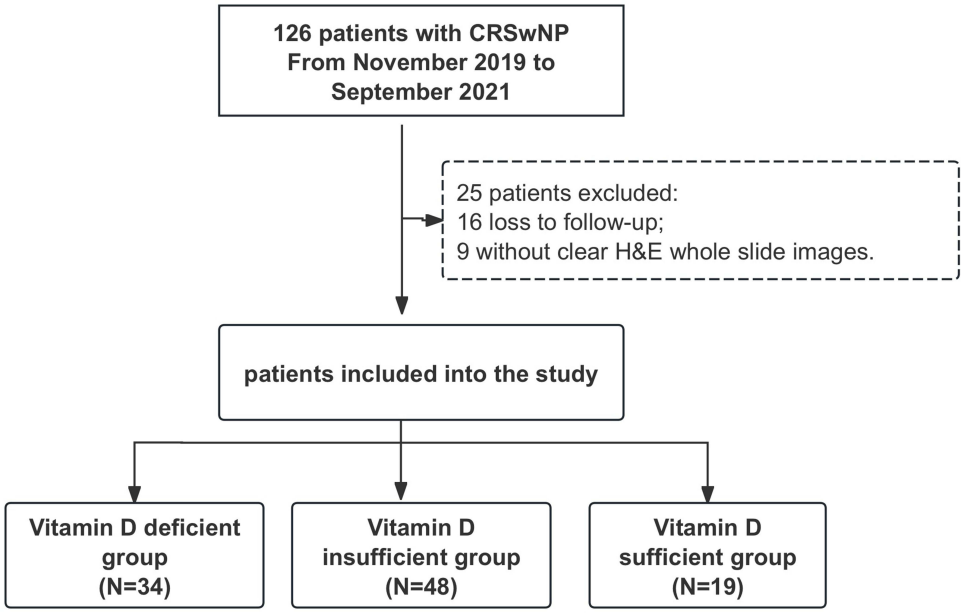

Figure 1 Flow Diagram of Patient Screening and Enrollment. In this study, we enrolled 101 patients with chronic rhinosinusitis with nasal polyps (CRSwNP). Based on serum vitamin D levels, patients were classified into three groups: vitamin D-deficient (n = 34), vitamin D-insufficient (n = 48), and vitamin D-sufficient (n = 19).

confirmed by two senior physicians according to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2020) criteria.[15] Patients were excluded if they met any of the following criteria: (1) incomplete clinical records, including missing tissue samples, baseline blood counts, nasal endoscopy videos, or computed tomography (CT) images; (2) use of topical intranasal corticosteroids within four weeks or systemic corticosteroids within twelve weeks prior to the initial blood draw; (3) presence of co-existing conditions such as fungal rhinosinusitis, cystic fibrosis, gastrooesophageal reflux, or sinonasal malignancy; or (4) missing post-operative follow-up data at the 12 month time point. Twenty-five patients were excluded, including 16 who were lost to follow-up and 9 with unavailable or poor-quality H&E whole-slide images. Ultimately, 101 patients were included in the final analysis. Based on serum vitamin D levels, patients were classified into three groups: vitamin D–deficient (n = 34), insufficient (n = 48), and sufficient (n = 19). A standardized data collection form was used to extract the following information: anonymised patient ID, gender, smoking status, comorbidities (asthma, allergic rhinitis), history of previous Endoscopic Sinus Surgery (ESS), and peripheral blood eosinophil count. Disease severity was assessed using the pre-operative Lund–Kennedy endoscopic score (LKS) and the Lund–Mackay CT score (LMS). Comorbid asthma was diagnosed based on the Global Initiative for Asthma (GINA 2010) guidelines,[16] and allergic rhinitis was defined according to the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria.[17] To ensure reliability, the LKS was calculated independently by two blinded investigators, and the results were averaged. The LMS was determined by consensus between a radiologist and a rhinologist, with a third senior reviewer consulted to resolve any discrepancies.[18]

This study was reviewed and approved by the Ethics Committee of Seventh Affiliated Hospital of Sun Yat-sen University (KY-2024-238-01). Written informed consent was obtained from all participants prior to their inclusion in the study.

Clinical Assessment and Patient's Follow-up

The symptom severity and treatment outcome were assessed in the cohort. The total nasal symptom score (TNSS) was calculated as the sum of scores for four individual symptoms, including nasal congestion, anterior rhinorrhea, postnasal drip, and loss of smell. These nasal symptoms were assessed using a scale of 0 = None, 1 = Mild, 2 = Moderate, or 3 = Severe. The TNSS used in our study was the instantaneous TNSS (iTNSS). The iTNSS score was calculated based on the severity of symptoms reported by the patient at the time of the clinic visit/data collection, reflecting the instantaneous status of the disease. Disease control was assessed according to the EPOS 2020 criteria,[15] with status classified as controlled, partly controlled, or uncontrolled. Two experienced otolaryngologists, blinded to patients' clinical and laboratory data, performed the classification independently. Discrepancies were resolved by consensus, and a third senior otolaryngologist was consulted if necessary.

Histopathologic Evaluation

Nasal polyp specimens were collected from all participants undergoing endoscopic sinus surgery. Consistent with prior studies,[19–21] a comprehensive histopathological assessment was performed to evaluate various tissue features. All histological evaluations were performed by two independent researchers who were blinded to the patients' clinical data, including serum vitamin D status and other clinical parameters. The assessment included evaluation and scoring of features such as basement membrane thickening, squamous metaplasia, subepithelial fibrosis, and goblet and gland cell densities. Additionally, mucosal ulceration, subepithelial edema, epithelial hyperplasia, Charcot-Leyden crystal (CLC) formation, and eosinophil aggregates were evaluated. The classification of basement membrane thickening was determined by thickness measurements and categorized as mild, moderate, or severe. Squamous metaplasia was quantified based on the proportion of metaplastic cells and categorized as none (no squamous cell metaplasia), mild (<50% squamous cell metaplasia), moderate (50–75% squamous cell metaplasia), or severe (>75% squamous cell metaplasia). Subepithelial fibrosis was classified as absent, present (mild; <50% of the field affected), or extensive (moderate to severe; ≥50% of the field affected). For the primary statistical analysis, fibrosis was analyzed using three groups—absent, mild (present), and extensive (combining moderate and severe)—to ensure sufficient statistical power and to highlight clinically significant pathological changes. At 400x magnification, counts were performed for goblet cells, total inflammatory cells, eosinophils, neutrophils, and gland cells. The severity of subepithelial edema was categorized into none, mild (focal edema, <10%), moderate (10–50%), and severe (diffuse edema >50% or polypoid changes). Both mucosal ulceration and epithelial hyperplasia, as well as CLC formation and eosinophil aggregates, were identified as

either present or absent. Eosinophil aggregates were specifically defined as one or more clusters of over 20 eosinophils per high power field within the lamina propria. For each nasal polyp specimen, counts were performed on three tissue blocks. In each block, five non-overlapping subepithelial fields were randomly selected for counting at 400× high-power field (HPF) using an ocular grid, and the mean number of cells per HPF was calculated for each cell type. All histological quantification was independently performed by two pathologists blinded to the clinical data and patients' vitamin D status. Inter-rater reliability was assessed on a random subset of 20% of slides using the intraclass correlation coefficient (ICC), which indicated excellent agreement (ICC = 0.85). Any remaining discrepancies were resolved by joint review.

Bulk RNA Sequencing for Nasal Polyps

Total RNA was extracted utilizing the TRIzol Reagent (Invitrogen, CA, USA) in accordance with the manufacturer's protocol. RNA purity and quantification were assessed using the NanoDrop 2000 spectrophotometer (Thermo Scientific, USA), and RNA integrity was verified using the Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara, CA, USA). Subsequently, RNA-seq library construction was performed using the VAHST Universal V6 RNA-seq Library Prep Kit, following the manufacturer's instructions. Transcriptome sequencing and subsequent analysis were carried out by OE Biotech Co., Ltd. (Shanghai, China). Sequencing was conducted on an Illumina NovaSeq 6000 platform, generating 150 bp paired end reads. Initial processing of raw reads in fastq format involved quality control using fastp, where low-quality reads were filtered out to produce clean reads. These clean reads were then aligned to the reference genome using HISAT2. Gene expression levels were quantified in terms of FPKM (Fragments Per Kilobase of transcript per Million mapped reads), and the read counts for each gene were determined using HTSeq-count.

Measurement of Serum 25-Hydroxyvitamin D Level

Prior to surgery, serum levels of 25-hydroxyvitamin D (25-(OH)D) were measured in all participants using an enzyme-linked immunosorbent assay (ELISA) provided by ALPCO Immunoassays (Salem, New Hampshire, USA). Based on the established guidelines, Vitamin D levels were categorized as follows: deficient (< 20 ng/mL), insufficient (20-< 30 ng/mL), and normal (≥ 30 ng/mL).[22] Patients were stratified into three vitamin D status groups (deficient, insufficient, and sufficient) for clinical and histological comparisons; however, for transcriptomic analysis, the insufficient and sufficient groups were consolidated into a single "non-deficient" reference group to enhance statistical power.

Statistical Analysis

Clinical and demographic data are presented as means with standard deviations (SD) or medians with interquartile ranges (IQR), as appropriate. The normality of data distribution was evaluated using the Shapiro–Wilk test. Univariate comparisons of normally distributed variables were conducted using *t*-tests, whereas the Mann–Whitney *U*-test was applied to non-normally distributed variables. Categorical variables were analyzed using Chi-square tests or Fisher's exact tests when appropriate. Because the proportional odds assumption was violated (test of parallel lines, $P < 0.05$), multinomial logistic regression is used to estimate category-specific associations between vitamin D deficiency and fibrosis severity. Fibrosis status (absent, present, or extensive) was included as the outcome variable, with "absent fibrosis" as the reference category. Vitamin D deficiency (yes/no) was included as the main predictor, and age (continuous) was adjusted for as a covariate. Results are reported as adjusted multinomial odds ratios (AOR) with 95% confidence intervals. All statistical analyses were performed using R software (Version 4.3.1). A two-sided $P < 0.05$ was considered statistically significant.

Transcriptomic data analysis was conducted using R software (Version 4.3.1). Differential expression was assessed using the DESeq2 R package. Principal component analysis (PCA) was utilized to confirm the biological replicates' consistency. Genes were considered significantly differentially expressed if they met the criteria of a padjust value less than 0.05 and an absolute fold change greater than 1.5. Cluster analysis of these differentially expressed genes (DEGs) was executed using the Pheatmap R package. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses of the DEGs were performed to identify significantly enriched terms, using the Clusterprofiler R package.

Results

General Characteristics of the Cohort

A total of 101 patients diagnosed with CRSwNP were included in the study. The cohort predominantly consisted of males (73.3%), with a mean age of 39.9 years. Among these patients, thirty-four (33.7%) had comorbid allergic rhinitis, and three (3.0%) had asthma. A subset of eight patients (7.9%) had undergone two or more sinus surgeries. Additionally, seven individuals (6.9%) were identified as current smokers. The subsequent research workflow was illustrated in Figure 2.

Clinical Features of Patients by Serum 25(OH)D Status

To evaluate the clinical implications of vitamin D status, patients were categorized into deficient, insufficient, and sufficient groups based on their serum 25(OH)D concentrations, with baseline characteristics presented in Table 1. The age of patients in the vitamin D-deficient group was significantly lower than that in the non-deficient group ($P = 0.017$). Furthermore, the Total Nasal Symptom Score (TNSS) was higher in the deficient group compared to the non-deficient group, although this difference approached but did not reach statistical significance ($P = 0.107$). No significant differences were observed between the groups in terms of gender, the presence of comorbid allergic rhinitis, comorbid asthma, history of prior sinus surgery, smoking history, and preoperative LMS. Additionally, eosinophil counts in peripheral blood and tissue, as well as tissue neutrophil counts, did not differ significantly across the groups. Similarly, there were no significant differences in disease control status among the groups.

Comparison of Histological Features Among CRSwNP Patients Stratified by Serum Vitamin D Status

To further characterize the pathohistological features of nasal polyp tissues in relation to vitamin D status, we performed a comprehensive comparative analysis of tissue structural characteristics among patients stratified into deficient, insufficient, and sufficient vitamin D groups. Subepithelial fibrosis differed significantly among the three vitamin D status groups ($P = 0.008$). Patients with vitamin D non-deficiency predominantly exhibited present (mild) fibrosis, whereas those with

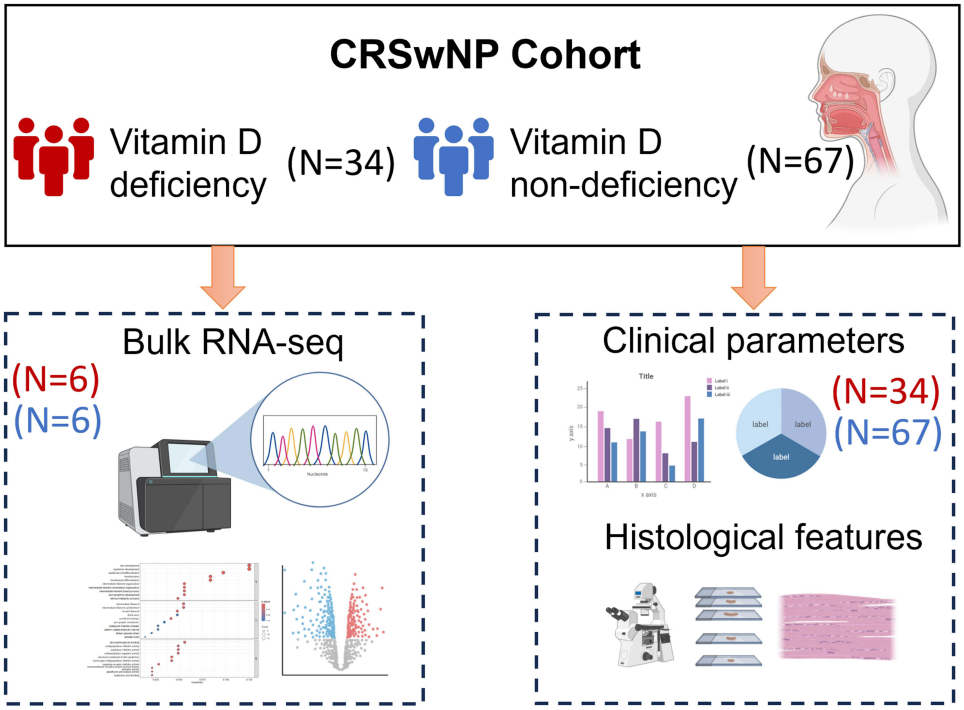

Figure 2 Workflow of study. The figure provides a visual summary of the methodology and analytical approach applied in the study. Initial analyses were performed on clinical parameters and histological features across the vitamin D-deficient (n = 34) and non-deficient groups (n = 67). Subsequently, from each cohort, six samples were carefully chosen for bulk RNA sequencing. This was followed by a comprehensive analysis of the transcriptomic expression profiles.

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Table 1 Clinical Characteristics of Patients Stratified by Serum 25(OH)D Status

Category	Deficient	Insufficient	Sufficient	*P* value
Subject, n	34	48	19	/
Male, n (%)	22 (64.7)	36 (75.0)	16 (84.2)	0.892
Age, mean (SD)	36.0 (10.2)	40.7 (9.4)	44.7 (14.8)	**0.017**
Smoke, n (%)	2 (5.9)	3 (6.3)	2 (10.5)	0.721
Prior sinus surgery, n (%)	2 (5.9)	5 (10.4)	1 (5.3)	0.721
Allergic rhinitis, n (%)	11 (32.4)	16 (33.3)	7 (36.8)	0.853
Asthma, n (%)	1 (2.9)	2 (4.2)	0 (0)	0.976
TNSS, mean (SD)	3.1 (1.8)	2.5 (2.0)	2.05 (1.6)	0.107
Preoperative L-K score, mean (SD)	7.1 (2.1)	6.6 (2.0)	6.7 (2.0)	0.604
Preoperative L-M CT score, mean (SD)	12.9 (5.1)	11.3 (5.2)	14.3 (4.0)	0.075
Blood eosinophil count, median (IQR) ($\times 10^9$/L)	0.32 (0.2)	0.38 (0.5)	0.28 (0.2)	0.503
Blood eosinophil percentage, median (IQR) (%)	4.7 (2.8)	4.0 (2.7)	4.2 (2.9)	0.64
Tissue eosinophil count, median (IQR) (/HPF)	12.6 (12.7)	8.3 (8.9)	12.5 (14.4)	0.178
Tissue eosinophil percentage, median (IQR) (%)	41.3 (30.6)	41. 6 (30.0)	42.1 (34.8)	0.995
Tissue neutrophil count, median (IQR) (/HPF)	29.9 (38.4)	17.5 (19.2)	25.7 (26.3)	0.14
Disease Control				0.18
Controlled, n (%)	5 (14.7)	15 (31.3)	5 (26.3)	
Partly Controlled, n (%)	20 (58.8)	26 (54.2)	13 (68.4)	
Uncontrolled, n (%)	9 (26.5)	7 (14.6)	1 (5.3)	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; IQR, Interquartile Range; L-K, Lund-Kennedy; L-M, Lund-Mackay; HPF, High Power Field; SD, Standard Deviation.

vitamin D-deficiency levels showed a higher proportion of extensive (moderate to severe) fibrosis. Representative histological images illustrating these differences are presented in Figure 3. Additionally, an increased thickness of the basement membrane was observed in the nasal polyps of in vitamin D sufficient and insufficient groups compared to the deficient group, although this variation did not reach statistical significance. Other histopathological features did not differ significantly across the three vitamin D status groups. Detailed results are provided in Table 2. After adjustment for potential confounders, including age, sex, season of blood sampling, smoking status, comorbid allergic rhinitis, comorbid asthma, and history of prior endoscopic sinus surgery, we initially fitted a multivariable ordinal logistic regression model with fibrosis grade as the outcome. However, the proportional odds assumption was violated (test of parallel lines, $P < 0.05$). Therefore, a multinomial logistic regression model was adopted as the final analytical approach, with "absent fibrosis" as the reference category. In the fully adjusted multinomial model, vitamin D deficiency was significantly associated with increased odds of mild (present) subepithelial fibrosis compared with absent fibrosis (adjusted OR 28.75, 95% CI 2.22–372.29, $P = 0.010$). In contrast, no statistically significant association was observed between vitamin D deficiency and extensive fibrosis. Other covariates, including age,

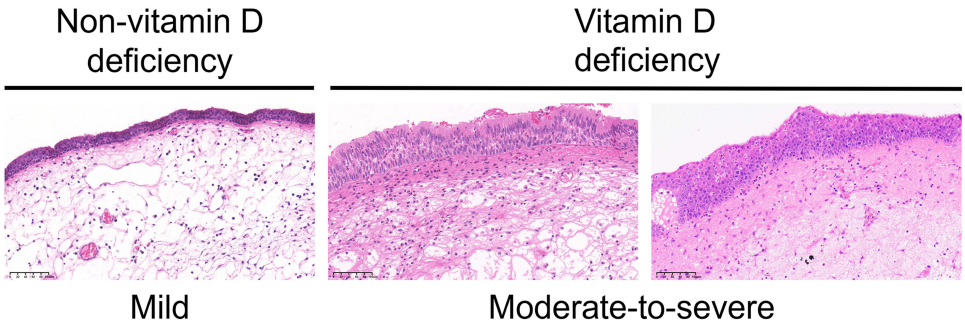

Figure 3 Representative histological images of subepithelial fibrosis in the vitamin D-deficient and non-vitamin D-deficient groups (H&E staining, 200×). The images from left to right show mild, moderate, and severe subepithelial fibrosis, respectively. Subepithelial fibrosis was classified as absent, present (mild; <50% of the field affected), or extensive (moderate to severe; ≥50% of the field affected). Moderate to severe fibrosis characterized by significant basement membrane thickening are predominantly observed in the vitamin D-deficient group.

Table 2 Histopathological Features of Nasal Polyps Stratified by Serum 25(OH)D Status

Category		Deficient	Insufficient	Sufficient	*P* value
Subject, n		34	48	19	–
Basement membrane thickening, n (%)	Mild (<7.5μm)	17 (50.0)	13 (27.1)	9 (47.4)	0.118
	Moderate (7.5–15μm)	17 (50.0)	32 (66.7)	10 (52.6)	
	Severe (>15μm)	0 (0.0)	3 (6.2)	0 (0.0)	
Squamous metaplasia, n (%)	None	25 (73.5)	44 (91.7)	15 (78.9)	0.289
	Present	9 (26.5)	4 (8.3)	4 (21.1)	
Subepithelial fibrosis, n (%)	None	1 (2.9)	8 (16.7)	5 (26.3)	**0.008**
	Present (mild)	26 (76.5)	27 (56.2)	7 (36.8)	
	Extensive (moderate/severe)	7 (20.6)	13 (27.1)	7 (36.8)	
Goblet cell number, median (IQR)	n/HPF	0.80 (3.2)	0.60 (3.4)	0.40 (5.2)	0.696
Gland number, median (IQR)	n/HPF	0.00 (0.2)	0.00 (1.6)	0.00 (0.8)	0.27
Mucosal ulceration, n (%)	None	28 (82.4)	43 (89.6)	17 (89.5)	0.594
	Present	6 (17.6)	5 (10.4)	2 (10.5)	
Subepithelial edema, n (%)	None	13 (38.2)	19 (39.6)	8 (42.1)	0.788
	Mild	5 (14.7)	12 (25.0)	1 (5.3)	
	Moderate	9 (26.5)	10 (20.8)	8 (42.1)	
	Severe	7 (20.6)	7 (14.6)	2 (10.5)	
Epithelial hyperplasia, n (%)	None	28 (82.4)	41 (85.4)	17 (89.5)	0.816
	Present	6 (17.6)	7 (14.6)	2 (10.5)	
Charcot–Leyden crystals, n (%)	None	32 (94.1)	45 (93.8)	18 (94.7)	1
	Present	2 (5.9)	3 (6.2)	1 (5.3)	
Eosinophil aggregates, n (%)	None	27 (79.4)	36 (75.0)	17 (89.5)	0.471
	Present	7 (20.6)	12 (25.0)	2 (10.5)	

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HPF, high power field; IQR, Interquartile Range.

sex, season of blood sampling, smoking status, comorbid allergic rhinitis, comorbid asthma, and prior endoscopic sinus surgery, were not significantly associated with fibrosis severity in either comparison. Complete model coefficients are presented in Table S1. Sensitivity and subgroup analyses were further performed to assess the robustness of the association between vitamin D deficiency and subepithelial fibrosis severity. Specifically, sensitivity analyses excluding participants aged <18 years (Table S2) and subgroup analyses restricted to non-smoking patients (Table S3) yielded results consistent with the primary analysis. In addition, exploratory analyses were conducted to evaluate the association between subepithelial fibrosis and disease outcomes (Table S4), as well as correlations between serum vitamin D levels and inflammatory biomarkers (Table S5); however, no statistically significant associations were observed in these analyses.

Gene Expression Profile Between Vitamin D Deficiency Group and Vitamin D Non-Deficiency Group

To explore the intrinsic transcriptomic differences between groups with and without vitamin D deficiency, we selected six samples from each group for comprehensive Bulk RNA sequencing (RNA-seq) analysis. Using Principal Component Analysis (PCA) and heatmap visualization, we discerned significant distinctions between the vitamin D-deficient and non-deficient groups (Figure 4a and b). Compared to the non-deficient group, the deficient group exhibited upregulation of 100 genes and downregulation of 68 genes (Figure 4c). Notably, in the vitamin D-deficient group, there was a significant upregulation of genes encoding collagen and fibrillin, specifically COL11A1, COL26A1, COL8A1, FBN1, COL1A2, and COL3A1. This upregulation correlates with enhanced tissue fibrosis in the vitamin D-deficient group relative to the non-deficient group. The genes that were significantly upregulated and downregulated are catalogued in Tables 3 and 4, respectively.

Furthermore, we conducted pathway enrichment analysis on the differentially expressed genes. In the Gene Ontology (GO) analysis for Biological Processes (BP), the upregulated genes in the vitamin D deficient group were significantly enriched in processes related to the extracellular matrix structure and organization. For the Cellular Component (CC)

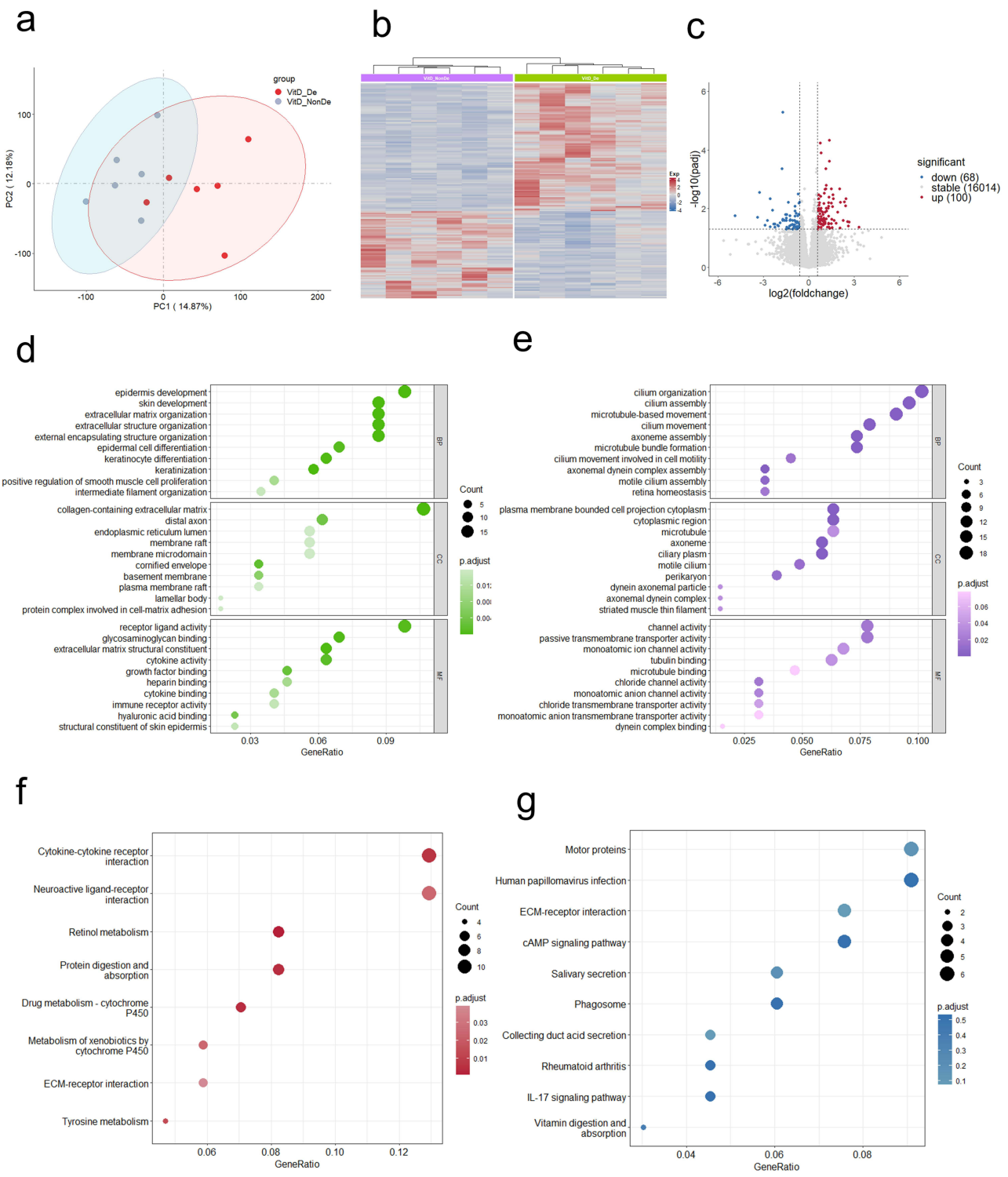

Figure 4 Transcriptomic analysis between vitamin D-deficient group and vitamin D non-deficient group. (**a**) Principal Component Analysis (PCA) of the samples from both groups, illustrating the distribution of variance. (**b**) Heatmap displaying the gene expression profiles of the vitamin D non-deficient and deficient groups, based on differentially expressed genes. (**c**) Volcano plot depicting the landscape of differentially expressed genes, with statistical significance plotted against fold-change values. (**d**) Gene Ontology (GO) enrichment analysis of significantly up-regulated genes. (**e**) GO enrichment analysis of significantly down-regulated genes. (**f**) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis for significantly up-regulated genes. (**g**) KEGG analysis for significantly down-regulated gene.

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Table 3 The Significantly up-Regulated Genes in the Vitamin D Deficient Group Compared to Non-Deficient Group

Gene_name	Gene_id	log2FoldChange	padj
LY6D	ENSG00000167656	3.32	0.043
KRT13	ENSG00000171401	2.68	0.029
KRT4	ENSG00000170477	2.61	0.039
CLCA2	ENSG00000137975	2.56	0.027
AKR1B10	ENSG00000198074	2.47	0.005
ATP13A5	ENSG00000187527	2.43	0.008
FGFBP1	ENSG00000137440	2.34	0.006
HSF5	ENSG00000176160	2.28	0.025
KCNIP1	ENSG00000182132	2.09	0.006
NMU	ENSG00000109255	2.07	0.045
KRT6C	ENSG00000170465	2.03	0.002
SERPINB13	ENSG00000197641	1.90	0.013
ALPK2	ENSG00000198796	1.80	0.032
FOSL1	ENSG00000175592	1.68	0.025
GPX2	ENSG00000176153	1.63	0.005
ITGBL1	ENSG00000198542	1.59	0.003
CEMIP	ENSG00000103888	1.56	0.009
KLK5	ENSG00000167754	1.54	0.044
TNC	ENSG00000041982	1.52	0.023
AFF2	ENSG00000155966	1.50	0.032
THBS2	ENSG00000186340	1.50	0.006
CYP26B1	ENSG00000003137	1.49	0.002
SYNDIG1	ENSG00000101463	1.38	0.046
LRP2	ENSG00000081479	1.37	0.000
TENM3	ENSG00000218336	1.36	0.000
MGARP	ENSG00000137463	1.34	0.004
B3GALT2	ENSG00000162630	1.33	0.043
CHRNB2	ENSG00000160716	1.32	0.031
GREM1	ENSG00000166923	1.31	0.008
NUDT10	ENSG00000122824	1.31	0.033
PAPPA	ENSG00000182752	1.31	0.006
COL11A1	ENSG00000060718	1.30	0.018
THBS1	ENSG00000137801	1.29	0.010
BRINP1	ENSG00000078725	1.22	0.043
CDH13	ENSG00000140945	1.17	0.012
COL26A1	ENSG00000160963	1.17	0.010
ST6GAL2	ENSG00000144057	1.16	0.002
EDIL3	ENSG00000164176	1.16	0.022
MATN3	ENSG00000132031	1.12	0.002
WISP1	ENSG00000104415	1.12	0.000
GJA1	ENSG00000152661	1.08	0.002
SVEP1	ENSG00000165124	1.08	0.013
LAMP5	ENSG00000125869	1.07	0.032
PCDH18	ENSG00000189184	1.07	0.029
NUTM2E	ENSG00000228570	1.02	0.025
TMEM158	ENSG00000249992	1.02	0.003
NID1	ENSG00000116962	1.01	0.032
COL8A1	ENSG00000144810	1.00	0.034
FBN1	ENSG00000166147	1.00	0.007
RORB	ENSG00000198963	0.99	0.021

(*Continued*)

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Table 3 (Continued).

Gene_name	Gene_id	log2FoldChange	padj
MERTK	ENSG00000153208	0.97	0.027
RIMBP2	ENSG00000060709	0.96	0.036
KRT5	ENSG00000186081	0.95	0.036
WNT5A	ENSG00000114251	0.94	0.016
FMN2	ENSG00000155816	0.93	0.013
ADAMTS2	ENSG00000087116	0.91	0.025
SLC5A3	ENSG00000198743	0.88	0.023
INHBA	ENSG00000122641	0.84	0.034
PRICKLE1	ENSG00000139174	0.83	0.000
MMP2	ENSG00000087245	0.82	0.043
CDH11	ENSG00000140937	0.81	0.012
AEBP1	ENSG00000106624	0.81	0.010
FADS1	ENSG00000149485	0.80	0.018
LRRC75A	ENSG00000181350	0.80	0.049
PDGFRA	ENSG00000134853	0.80	0.023
HEPH	ENSG00000089472	0.79	0.004
TNFRSF11B	ENSG00000164761	0.79	0.033
FADS2	ENSG00000134824	0.78	0.025
MTCL1	ENSG00000168502	0.78	0.024
SPON2	ENSG00000159674	0.78	0.025
DKK3	ENSG00000050165	0.76	0.000
PDGFRB	ENSG00000113721	0.76	0.026
PLXDC2	ENSG00000120594	0.75	0.025
GSDME	ENSG00000105928	0.75	0.011
PRRX1	ENSG00000116132	0.74	0.030
THY1	ENSG00000154096	0.74	0.015
RERG	ENSG00000134533	0.73	0.049
LAMB1	ENSG00000091136	0.73	0.023
COL1A2	ENSG00000164692	0.72	0.049
RYR1	ENSG00000196218	0.71	0.006
HPSE	ENSG00000173083	0.71	0.025
THSD4	ENSG00000187720	0.71	0.030
SORCS2	ENSG00000184985	0.71	0.045
EFEMP1	ENSG00000115380	0.68	0.023
RGL1	ENSG00000143344	0.67	0.007
TNS3	ENSG00000136205	0.67	0.005
ROR2	ENSG00000169071	0.67	0.012
PTPN13	ENSG00000163629	0.67	0.025
KIRREL1	ENSG00000183853	0.65	0.003
XPC	ENSG00000154767	0.65	0.010
RAB7B	ENSG00000276600	0.65	0.029
SYNC	ENSG00000162520	0.64	0.029
PCDHGC3	ENSG00000240184	0.63	0.011
HEG1	ENSG00000173706	0.63	0.023
CLMP	ENSG00000166250	0.63	0.041
PDZD2	ENSG00000133401	0.62	0.018
LRP1	ENSG00000123384	0.62	0.010
COL3A1	ENSG00000168542	0.62	0.049
LOXL1	ENSG00000129038	0.60	0.034
TEX2	ENSG00000136478	0.60	0.023

Table 4 The Down-Regulated Genes in the Vitamin D Deficient Group Compared to Non-Deficient Group

Gene_name	Gene_id	log2FoldChange	padj
MEPE	ENSG00000152595	−4.86	0.017
BPIFB6	ENSG00000167104	−3.39	0.020
ALAS2	ENSG00000158578	−3.26	0.003
MUC19	ENSG00000205592	−2.89	0.036
SLC22A31	ENSG00000259803	−2.72	0.025
CDH15	ENSG00000129910	−2.54	0.042
SFTPB	ENSG00000168878	−2.54	0.005
CGREF1	ENSG00000138028	−2.39	0.011
PMP2	ENSG00000147588	−2.32	0.033
DLK1	ENSG00000185559	−2.23	0.043
C1QTNF8	ENSG00000184471	−2.23	0.034
HBB	ENSG00000244734	−2.07	0.036
C1orf141	ENSG00000203963	−2.00	0.039
CILP2	ENSG00000160161	−1.91	0.030
CLCNKB	ENSG00000184908	−1.78	0.000
CLCNKA	ENSG00000186510	−1.71	0.000
BSND	ENSG00000162399	−1.70	0.025
PRPH	ENSG00000135406	−1.70	0.023
TDRD5	ENSG00000162782	−1.57	0.025
FOXI2	ENSG00000186766	−1.54	0.016
DOC2A	ENSG00000149927	−1.49	0.049
PCP2	ENSG00000174788	−1.48	0.025
GPAT2	ENSG00000186281	−1.47	0.021
PTH2R	ENSG00000144407	−1.45	0.042
FYB2	ENSG00000187889	−1.45	0.016
RNF224	ENSG00000233198	−1.44	0.045
COL9A3	ENSG00000092758	−1.34	0.006
KCNK15	ENSG00000124249	−1.32	0.046
CXXC4	ENSG00000168772	−1.28	0.049
WDR97	ENSG00000179698	−1.27	0.038
ZNF727	ENSG00000214652	−1.25	0.017
AQP7	ENSG00000165269	−1.24	0.025
TCTEX1D2	ENSG00000213123	−1.22	0.024
COL11A2	ENSG00000204248	−1.20	0.036
HES6	ENSG00000144485	−1.10	0.034
CD164L2	ENSG00000174950	−1.07	0.049
ATP6V1C2	ENSG00000143882	−1.06	0.025
SMIM5	ENSG00000204323	−1.03	0.047
MT-ND6	ENSG00000198695	−1.00	0.035
CCNO	ENSG00000152669	−0.99	0.036
GPT	ENSG00000167701	−0.99	0.045
WFDC2	ENSG00000101443	−0.98	0.039
MISP3	ENSG00000141854	−0.94	0.025
WIPF3	ENSG00000122574	−0.94	0.035
RHPN1	ENSG00000158106	−0.91	0.012
KCNIP2	ENSG00000120049	−0.91	0.018
TSTD1	ENSG00000215845	−0.90	0.026
SMIM22	ENSG00000267795	−0.90	0.008
HSF4	ENSG00000102878	−0.86	0.043
FP565260.6	ENSG00000280433	−0.85	0.029

(*Continued*)

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Table 4 (Continued).

Gene_name	Gene_id	log2FoldChange	padj
AATK	ENSG00000181409	−0.84	0.014
HSD11B1L	ENSG00000167733	−0.83	0.042
NPDC1	ENSG00000107281	−0.81	0.030
TDRP	ENSG00000180190	−0.80	0.049
ERICH2	ENSG00000204334	−0.80	0.045
IRX3	ENSG00000177508	−0.77	0.040
D2HGDH	ENSG00000180902	−0.77	0.028
KIFC2	ENSG00000167702	−0.74	0.048
CFAP298	ENSG00000159079	−0.73	0.029
PPP1R16A	ENSG00000160972	−0.72	0.017
GIPC2	ENSG00000137960	−0.69	0.003
ARPC1A	ENSG00000241685	−0.67	0.031
INHBB	ENSG00000163083	−0.64	0.039
TRADD	ENSG00000102871	−0.64	0.015
HDHD3	ENSG00000119431	−0.63	0.006

category, these genes predominantly related to the collagen-containing extracellular matrix. In terms of Molecular Function (MF), the focus was on the structural constituents of the extracellular matrix (Figure 4d). Conversely, the significantly downregulated genes were primarily involved in pathways associated with axoneme assembly, microtubule bundle formation, and cilium movement, among other relevant GO pathways (Figure 4e). Detailed results of these significant GO enrichment pathways are provided in Table S6 and S7.

Additionally, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis revealed that ECM-receptor interaction was a prominent pathway enriched with upregulated genes in the vitamin D deficient group (Figure 4f). The analysis of pathways enriched with downregulated genes highlighted the vitamin digestion and absorption pathway (Figure 4g). Comprehensive details on the KEGG enrichment pathways are documented in Table S8 and S9. This extensive analysis underscores the molecular alterations induced by vitamin D deficiency and highlights potential targets for further investigation and therapeutic intervention.

Discussion

Our integrated histopathological and transcriptomic analysis demonstrates that vitamin D deficiency in CRSwNP is more strongly correlated with subepithelial fibrosis than with inflammatory infiltration. Histological analysis revealed that vitamin D-deficient patients had a significantly higher incidence of subepithelial fibrosis. Meanwhile, transcriptomic profiling indicated altered expression of genes enriched in extracellular matrix organization pathways, which was consistent with the observed structural changes. Together, these findings indicate that vitamin D deficiency correlates preferentially with tissue remodeling rather than inflammatory burden in nasal polyps. This positions subepithelial fibrosis as a previously under-appreciated pathological hallmark of vitamin D-deficient CRSwNP. Building on previous reports that vitamin D exerts important immunomodulatory effects and is implicated in the pathophysiology of nasal polyps,[23–25] our study provides the first systematic evidence linking low vitamin D status specifically to a fibrosis-predominant disease phenotype.

Histopathological analysis identified subepithelial fibrosis as the most prominent feature associated with vitamin D deficiency, whereas epithelial injury and inflammatory cell infiltration did not differ significantly between groups. Changes in histopathological structures are often closely associated with pathogenesis and inflammatory characteristics.[20,26–28] Consistently, transcriptomic profiling revealed differential expression of genes involved in extracellular matrix (ECM) organization, collagen synthesis, and fibroblast growth factor–related pathways. This concordance between structural and molecular findings supports the notion that vitamin D deficiency is preferentially associated with tissue remodeling rather than inflammatory burden, in line with previous reports linking low vitamin D levels to enhanced fibrosis in CRSwNP.[14,29] This

pattern suggests that vitamin D deficiency may be linked to altered stromal cell behavior and fibrogenic signaling thresholds without necessarily altering inflammatory cell recruitment, thereby uncoupling tissue remodeling from overt inflammation.

Clinically, while previous studies have reported more severe disease manifestations in vitamin D-deficient CRSwNP patients,[30,31] our findings suggest that the impact of vitamin D status on symptom severity and postoperative outcomes may be limited at the clinical level in our cohort. Notably, despite comparable clinical presentations between groups, pronounced differences were observed at the histological and transcriptomic levels, supporting the concept that tissue remodeling may precede overt clinical deterioration. The observed age difference between groups likely reflects baseline cohort characteristics rather than an independent association with vitamin D status and was accounted for in subsequent analyses.

Despite similar clinical presentations across vitamin D status groups, our comprehensive histological and transcriptomic analyses revealed a distinct ECM-enriched molecular signature exclusively in vitamin D-deficient nasal polyps, consistent with enhanced fibrotic remodeling. This suggests that vitamin D deficiency may be linked to early structural changes even without evident clinical deterioration. This profibrotic phenotype arises within the characteristic immunological context of East Asian CRSwNP, where inflammation typically exhibits a mixed Th1/Th17 pattern rather than the Th2-dominant profile observed in Western populations. In this context, vitamin D deficiency may predominantly affect tissue remodeling pathways rather than classical inflammatory responses. Although causality cannot be inferred from our observational data, existing evidence provides a plausible mechanism. The vitamin D active metabolite, $1,25(OH)_2D$, modulates TGF-β/SMAD2/3 signaling, thereby limiting myofibroblast differentiation and excessive ECM deposition;[32–34] thus, Vitamin D deficiency may blunt these antifibrotic effects, fostering a profibrotic microenvironment. Beyond its role in fibroblast regulation, vitamin D contributes to the maintenance of epithelial barrier integrity, promotes tissue repair,[36] and inhibits epithelial–mesenchymal transition.[37] Respiratory epithelial cells are also capable of locally converting inactive vitamin D into its active form, enabling site-specific regulation of host defense mechanisms.[38] In parallel, vitamin D signaling has been shown to suppress TLR4/NF-κB–mediated inflammatory responses in respiratory epithelial cells and to enhance glucocorticoid-mediated anti-inflammatory effects.[39] Furthermore, clinical evidence suggests that variations in vitamin D receptor signaling are associated with glucocorticoid responsiveness in airway diseases.[35] Collectively, these mechanisms offer a biologically plausible explanation for the structural changes observed in vitamin D-deficient CRSwNP, even when there is no significant clinical deterioration.

This study has several strengths. First, we integrated structured histopathological assessment with transcriptomic profiling, enabling a robust evaluation of tissue remodeling and its molecular correlates. Second, by focusing on subepithelial fibrosis rather than inflammatory cell infiltration alone, we addressed a clinically relevant but underexplored aspect of CRSwNP pathophysiology. Third, our analysis was conducted in an East Asian CRSwNP cohort, providing insights into the role of vitamin D within a non–Th2-dominant inflammatory context.

Despite these strengths, several limitations warrant acknowledgment. First, the sample size was relatively modest, and our findings have not yet been validated in a larger, independent external cohort. The wide confidence intervals observed for the association between vitamin D deficiency and mild fibrosis likely reflect the limited number of cases within specific histological strata; thus, these results should be interpreted with caution. Future studies with larger multi-center cohorts are needed to validate our findings and enhance their generalizability. Second, the scale of the transcriptomic sequencing was constrained, necessitating further validation in larger cohorts to confirm the molecular signatures identified. Subsequent studies with deeper transcriptomic profiling or single-cell sequencing could further refine the ECM-enriched molecular signature identified herein. Third, as a retrospective clinical study, it lacks direct experimental evidence (eg, in vitro or in vivo models) to establish a definitive causal link and elucidate the precise immunomodulatory mechanisms through which vitamin D deficiency drives tissue fibrosis in nasal polyps. Furthermore, the absence of patient-reported outcome measures, such as the 22-item Sinonasal Outcome Test (SNOT-22), limits our ability to assess the long-term clinical burden and health-related quality of life. Additionally, key physiological determinants of serum vitamin D levels, including body mass index (BMI) and sunlight exposure, were not systematically recorded, which may have introduced residual confounding or affected the precision of our estimates. Regarding lifestyle factors, although sensitivity analyses excluding smokers yielded consistent results, cigarette smoking remains a potential confounder. Due to the inherent limitations of retrospective data, we lacked a refined stratification of smoking exposure (eg, pack-years), highlighting the need for prospective studies with more precise, longitudinal assessments. Finally, the findings may be subject to regional bias, highlighting the need for multi-center, cross-geographical comparative research to confirm the universality of our conclusions.

Conclusion

In conclusion, vitamin D deficiency was associated with specific histological features, particularly subepithelial fibrosis, in patients with CRSwNP. Transcriptomic analysis further revealed distinct gene expression profiles in the vitamin D–deficient group, with enrichment of extracellular matrix–related pathways. Our findings support a potential link between vitamin D status and fibrotic tissue remodeling in CRSwNP, suggesting that vitamin D deficiency may characterize a subset of patients with a more pronounced fibrotic phenotype. Further mechanistic studies using in vitro and animal models are warranted to elucidate the direct role of vitamin D in regulating fibroblast activity and extracellular matrix deposition. Prospective clinical studies are also needed to determine whether modulation of vitamin D status could influence disease course or postoperative outcomes in CRSwNP.

Data Sharing Statement

The datasets are available from the corresponding author upon reasonable request. The accession number of raw sequencing data from nasal polyp samples in this study is GSA (Genome Sequence Archive) HRA007203.

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Author Contributions

Mengshi Chi: Conceptualization, data collection, data curation, formal analysis, investigation, methodology, writing – original draft. Kanghua Wang: Data curation, validation, visualization, writing – review & editing. Mingmin Bi: Data collection, data curation, validation, writing – review & editing. Zheng Yang: Investigation, methodology, quality control, writing – review & editing. Yuhan Xing: Conceptualization, supervision, writing – review & editing. Yunping Fan: Conceptualization, funding acquisition, resources, supervision, writing – review & editing. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work. All authors have agreed on the journal to which the article will be submitted. Mengshi Chi and Kanghua Wang contributed equally to this work as co-first authors. Yuhan Xing and Yunping Fan contributed equally to this work as co-corresponding authors.

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Disclosure

The author(s) report no conflicts of interest in this work.

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