Is Nasal Polyposis Related to Levels of Serum Vitamin D and Vitamin D Receptor Gene Expression?

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Background: Nasal polyposis (NP) is the most frequent cause of nasal masses. Despite considerable research on the subject, its etiology has not been fully elucidated, and effective treatment methods have not been developed. Some etiological factors causing low or high expression of genes in genetically predisposed individuals may play a role in the pathogenesis of the disease. The purpose of this study was to assess the relation between levels of vitamin D receptor (VDR) gene expression and serum vitamin D with NP.

Material/Methods: The study included 46 subjects with NP (NP group) and 40 volunteers (control group). Nasal polyp tissue samples were taken from the NP group and nasal mucosa samples were taken from the control group. Levels of VDR gene expression in the tissue samples were assessed using the real-time polymerase chain reaction (RT-PCR) method.

Results: Mean serum 25(OH)D levels were 13.38±14.08 ng/ml in the NP group and 10.57±6.44 ng/ml in the control group (p=0.249). VDR gene expression was present in 17.5% of the NP group and 3.3% of the control group, and the difference between the 2 groups was statistically significant (likelihood ratio $\chi^2=3.887$; $p=0.049$).

Conclusions: This is the first study to assess levels of VDR gene expression in subjects with NP. Our results suggest that VDR gene expression may be associated with the pathogenesis or progression of NP.

MeSH Keywords: Calcifediol • Gene Expression • Nasal Polyps

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Nasal polyposis (NP), an inflammatory disorder of nose and paranasal sinuses, is the most frequent reason of nasal masses [1]. The prevalence of NP in general population ranges between 1% and 4%. Although NP occurs in both sexes and in all age groups, it is most frequently seen in the 4th and 5th decades of life [2,3].

The etiology of NP is not fully understood; however, it is related to bronchial asthma and aspirin intolerance at rates of 31–40% and 6%, respectively [4]. The role of genetics in etiology has been investigated by many studies due to presence of NP history in family members of the patients. Molnar-Gabor et al. have reported that cases with HLA-DR7-DQA1 and HLA-DQB1 haplotypes are at 2–3 times greater risk for NP [5].

The vitamin D receptor (VDR) is a member of the steroid receptor family [6]. The gene of VDR is a protein of about 60 kDa molecular weight, made of 427 amino acids, and localized in the region of human chromosome 12q13-14 [7]. Active vitamin D receptors are widely present in many different tissues, such as those of hypophysis, ovaries, skin, stomach, pancreas, thymus, breasts, kidneys, parathyroid glands, and peripheral leukocytes [8]. It has been reported that small changes in the function or structure of VDR molecule can lead to changes in cell and tissue homeostasis [9].

Vitamin D plays an important role in immune regulation. Locally synthesized 25 (OH) vitamin D [25(OH)D] regulates immune response with paracrine effect. The 25(OH)D shows its immunomodulatory effect by regulating the transcriptions of genes mediating biologic effects after binding to nuclear VDRs present in many cell types, such as monocytes, macrophages, dendritic cells, and immune system cells, including activated T and B cells [10]. Active vitamin D [1,25(OH)2D] controls more than 200 genes directly or indirectly responsible for regulation of cell proliferation, differentiation, apoptosis, and angiogenesis [11,12].

The relationship of VDR gene expression with inflammatory pathologies such as rheumatoid arthritis, gastrointestinal inflammation, obesity, and inflammasome activity has been demonstrated in various studies [13–15], but no published study has explored the relationship between VDR gene expression and expression of nasal polyposis.

It has been reported that inflammation plays a role in the pathogenesis of nasal polyposis [1]. The aim of this study was to evaluate the relationship of VDR gene expression, which is related to various inflammatory pathologies with NP.

### Material and Methods

#### Subjects

This prospective study involved 86 cases referred to the Otorhinolaryngology Clinic of our hospital between October 2014 and March 2015 (mean age: 34.97±12.75, range: 18–64 years). Written informed consent was obtained from all participants. The study protocol was approved by the local ethics committee (approval identification number: 16.10.2014-02). The study was funded by the Science Research Supporting Agency (BAP) (project number 2015-TF-U006). The NP group comprised chronic sinusitis patients with polyps using the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) criteria [16]. Cases diagnosed as allergic rhinitis were not included to the study [17].

The NP group comprised 46 consecutive subjects who were diagnosed as having NP by punch biopsy and who underwent surgery. Forty volunteers who were operated on due to septal deviation without nasal mucosal inflammatory pathology and chronic systemic disorder served as the control group.

Subjects with pathologies that can cause nasal mass, such as inverted papilloma, antrochoanal polyp, carcinomas, sarcomas, encephalocele, pyogenic granuloma, and angiofibroma, were not included in the study. We also excluded subjects with a Churg–Strauss syndrome, cystic fibrosis, Kartagener’s syndrome, severe immunodeficiency, asthma, acetylsalicylic acid (ASA) sensitivity, chronic systemic diseases (e.g., diabetes mellitus, hypertension, and chronic renal insufficiency), history of vitamin D therapy, rachitis, osteoporosis, osteomalacia, Paget’s disease, or history of another metabolic bone disorder.

#### Serum 25(OH)D measurements

Serum 25(OH)D levels were assessed with chemiluminescence (spectrophotometry) method by using the ROCHE HITACHI COBAS E 601 (Germany) device. Nasal polyp and control groups were divided into subgroups according to serum 25(OH)D levels. Based on Endocrine Society Clinical Practice Guidelines [18], serum 25(OH)D level ≤20 ng/mL was accepted as vitamin D deficiency, 21–29 ng/mL as vitamin D insufficiency, and ≥30 ng/mL as normal.

#### Tissue samples

The levels of VDR gene expression were assessed in the subjects’ nasal polyp tissue surgically extirpated and in nasal mucosal specimens taken during septoplasty from the controls, by using the real-time polymerase chain reaction (RT-PCR) method. Tissue samples were washed in physiological saline and immediately frozen in liquid nitrogen. Tissue samples were collected during septoplasty from the controls, by using the real-time polymerase chain reaction (RT-PCR) method. Tissue samples were washed in physiological saline and immediately frozen in liquid nitrogen. Tissue samples were collected during septoplasty from the controls, by using the real-time polymerase chain reaction (RT-PCR) method. Tissue samples were washed in physiological saline and immediately frozen in liquid nitrogen.
were maintained at –80ºC until analysis. Because of insufficient quantity of specimen, VDR gene expression could not be assessed in 6 subjects with nasal polyps and in 10 controls. Thus, VDR gene expression levels could be determined in 40 subjects with nasal polyps and 30 controls.

Real-time PCR

Nasal polyp tissues were obtained from subjects during nasal polyp surgery. In the control group, nasal mucosa tissues were collected from healthy volunteers via nasal mucosa biopsy. Total RNA nasal polyp patterns were attained by using a High Pure PCR RNA Tissue Kit (Roche, Germany). The purity of the RNA was identified by the 260/280 absorbance rate on a NanoDrop device. The entirety of total refined RNA was controlled by denaturing agarose gel electrophoresis and ethidium bromide staining. In initial-band cDNA synthesis, a stable quantity of 1 μg of total RNA was reverse-transcribed utilizing random hexamers as primers and Transcriptor Reverse Transcriptase (Roche, Mannheim, Germany). Gene expression was studied by real-time PCR by using the LightCycler® 480 II Real-time PCR System for testing of VDR gene expression. The reaction was implemented, following the manufacturer’s protocol, in a final volume of 25 μL. The cycle program consisted of a first denaturing of 10 min at 95ºC, then 40 cycles of 10 s denaturing stage at 95ºC, 30 s hardening stage at 60ºC, and 1 min enlarging stage at 72ºC. Commercially available and pre-validated TaqMan primer/probe tools utilized in human nasal polyp specimens used the VRD gene as a target gene and β-actin gene was utilized as endogenous control for the target gene in every reaction. A threshold cycle (Ct value) was attained for every amplification curve and a ΔCt value was first counted by subtracting the Ct value for human β-actin cDNA from the Ct value for every specimen and transcript. Fold-change compared to the endogenous control were later detected by counting 2-ΔCt, and expression is stated as the expression rate relative to β-actin gene expression for humans, following the manufacturer’s guidelines. Inter-assay variation (coefficient of variation) of the housekeeping gene was less than 0.5%. All specimens were measured in triplicate and positive and negative controls were used in all the reactions.

Statistical analysis

Descriptive statistics of studied variables (characteristics) are presented as mean and standard deviation for continuous variables and as count and percent for categorical variables. We used the t test to compare study group means. Comparisons of individuals having VDR gene expression between control and nasal polyp groups were analyzed by using χ² and likelihood ratio tests. Because of the possible decrease by the power of chi-square (χ²) testing due to the expectation that the value of the frequency of VDR positivity was lower than 5, the P value produced by the likelihood ratio test was considered instead. In addition, the Z test was also used to compare 2 proportions. Statistical significance level was set at 5% and the SPSS (ver: 13) statistical program was used for all statistical computations.

Results

The mean ages of the control and NP group were 35.58±14.26 and 34.30±11.6, respectively. Males formed 60% of the control

Table 1. Demographic and laboratory datas for study groups.

|                  | Control (n=40) | Nasal polyp (n=46) | p     |
|------------------|---------------|--------------------|-------|
| Mean age ± SD    | 35.58±14.26   | 34.30±11.6         | 0.609 |
| Male/Female      | 24/16         | 31/15              | 0.476 |
| 25(OH)D (ng/ml) ± SD | 10.57±6.44   | 13.38±14.08        | 0.249 |

25(OH)D – 25 (OH) vitamin D, SD – standart deviation.

Table 2. Comparison of the nasal polyp and control groups according to 25(OH)D subgroups.

| 25(OH)D subgroups | Control (n=40) | Nasal polyp (n=46) | p     |
|-------------------|---------------|--------------------|-------|
| Deficiency (≤20 ng/ml) | 35 (84.5%) | 40 (86.9%)         |       |
| Insufficiency (21–29 ng/ml) | 5 (12.5%) | 2 (4.4%)          |       |
| Normal (≥30 ng/ml) | 0 (0%)        | 4 (8.9%)           |       |

χ²=5.226; p=0.073.

25(OH)D – 25 (OH) vitamin D.
group and 67.3% of the NP group. There was no significant difference between the 2 groups in terms of age or sex (Table 1).

**Serum 25(OH)D levels**

The mean levels of serum 25(OH)D in the control group and NP group were 10.57±6.44 ng/mL and 13.36±14.08 ng/mL, respectively. There was no significant difference in serum 25(OH)D levels between the 2 groups (p=0.249) (Table 1). There was also no significant difference between the NP group and control group in terms of subgroups based on 25(OH)D levels ($\chi^2=5.226; p=0.073$) (Table 2).

**VDR gene expression**

The VDR gene expression levels could be determined in 40 cases in the NP group and in 30 cases in the control group. The measurement values of VDR gene expression in both groups are shown in Table 3.

Vitamin D receptor gene expression was present in 7 (17.5%) of the NP group (n=40) and in 1 (3.3%) of the control group (n=30), and the difference between the 2 groups was statistically significant (likelihood ratio $\chi^2=3.887; p=0.049$) (Table 4).

The relationship of the presence of VDR gene expression with age, sex, and serum 25(OH)D levels is shown in Table 5. There was no statistically significant difference between VDR gene expression-positive and -negative cases in terms of age, sex, or serum 25(OH)D levels.

**Discussion**

According to the concept of united airways, the respiratory system is a functional unit that includes the nose, paranasal sinuses, larynx, trachea, bronchi, and bronchiole. Disorders affecting the lower segments of the respiratory tract may cause similar disorders of similar pathophysiology in other parts of the tract [19]. In recent years, many studies have investigated the role of vitamin D in the pathophysiology of chronic inflammatory respiratory disorders such as allergic rhinitis, chronic rhinosinusitis, and asthma. For instance, vitamin D deficiency is associated with the severity of asthma and pulmonary function [20–23]. Maternal vitamin D intake from diet throughout pregnancy may be negatively related to risk of asthma and allergic rhinitis in childhood [24].

There have been various studies in the literature on the relationship between vitamin D and NP. Vitamin D derivatives can prevent human nasal polyp-derived fibroblast proliferation in cultured cell models, and regulated on activation normal T cell expressed and -secreted (RANTES) and matrix metalloproteinase 9 produced in keratinocytes and interleukin-8 production in normal human dermal fibroblasts [25–27]. Some recent studies indicated that vitamin D deficiency is related to disease severity and might be a key player in the etiopathology of chronic rhinosinusitis with NP [28–30]. Hu et al. reported that polymorphisms in CYP2R1-rs10766197 and DHCR7/NADSYN1-rs12785878 are associated with vitamin D deficiency in Uygur and Kazak ethnic populations [31]. In the present study, we did not determine statistically different differences between the NP group and control group, and there was no statistically significant difference between the 2 groups in distribution of serum vitamin D subgroups. These findings indicate that there is no direct relationship between NP and serum vitamin D levels. We also found low mean values of 25(OH)D in both groups, perhaps due to the time period when the study was conducted (October–March), during which there is less exposure of skin to sunlight in the region, and insufficient intake of vitamin D in the diet because of low socio-economic conditions [33,34].

Many studies in the literature have investigated serum vitamin D levels in NP. To the best of our knowledge, there is no study in the literature on VDR gene expression in NP subjects. It has been previously reported that serum 25(OH)D levels in chronic rhinosinusitis with NP cases were importantly lower than those in chronic rhinosinusitis without NP cases [30]. Furthermore, the serum 25(OH)D level was remarkably and inversely associated with the size of nasal polyps. As vitamin D is known to have immunomodulatory influences on a variety of immune cells, these findings demonstrate that low vitamin D levels might fail to reduce cytokine emission from inflammatory cells, due to constitutive activation of the inflammatory cascade [35,36]. A previous study showed an important dose-related decrease in nasal polyp-derived fibroblast proliferation when the cells were treated with different doses of calcitriol and tacalcitol [25]. Rostkowska-Nadolska et al. also demonstrated that calcitriol and tacalcitol prevented the synthesis of the proinflammatory cytokines interleukin-6 and interleukin-8 in nasal polyp fibroblast cultures [37].

Cavalcanti et al. determined a relationship between the VDR gene with rheumatoid arthritis in the Brazilian population. They stated that their results support the role of the VDR gene in susceptibility to RA [13]. Furthermore, Al-Daghri et al. reported that VDR gene expression is associated with obesity and inflammatory activity. They also reported that the vitamin D/VDR axis played a role in obesity, associated with ongoing inflammation, possibly resulting from alterations in gut permeability and microbial translocation. In addition, they speculated that these results could help the definition of VDR fingerprints that predict an increased risk of developing obesity, and may contribute to the identification of novel therapeutic strategies for this metabolic condition [14]. In another study, it was reported that VDR gene expression is related to
| Nasal polyp group (n=46) (Patient No.) | Age | Gender | 25(OH)D expression value | VDR gene expression value | Control group (n=40) (Case No.) | Age | Gender | 25(OH)D expression value | VDR gene expression value |
|--------------------------------------|-----|--------|--------------------------|--------------------------|--------------------------------|-----|--------|--------------------------|--------------------------|
| 1                                   | 42  | M      | 4.55                     | 0                        | 1                             | 19  | F      | 7.39                     | IS                       |
| 2                                   | 48  | M      | 7.75                     | IS                       | 2                             | 18  | M      | 19.12                    | 0                       |
| 3                                   | 28  | M      | 4.90                     | 0                        | 3                             | 18  | M      | 11.70                    | 0                       |
| 4                                   | 51  | M      | 6.10                     | 0                        | 4                             | 47  | M      | 9.76                     | 0                       |
| 5                                   | 18  | F      | 4.77                     | 3.30                     | 5                             | 35  | M      | 8.44                     | 0                       |
| 6                                   | 39  | M      | 6.88                     | 0                        | 6                             | 22  | F      | 3.38                     | IS                      |
| 7                                   | 37  | M      | 7.25                     | 0                        | 7                             | 18  | M      | 4.07                     | 0                       |
| 8                                   | 25  | M      | 8.77                     | 0                        | 8                             | 37  | M      | 12.08                    | 0                       |
| 9                                   | 26  | M      | 11.14                    | 0                        | 9                             | 46  | M      | 12.14                    | 0                       |
| 10                                  | 27  | M      | 11.25                    | 0                        | 10                            | 18  | M      | 25.18                    | 0                       |
| 11                                  | 47  | M      | 11.55                    | 0                        | 11                            | 25  | M      | 6.64                     | 0                       |
| 12                                  | 56  | M      | 17.46                    | 9.20                     | 12                            | 40  | F      | 6.32                     | IS                      |
| 13                                  | 49  | M      | 11.87                    | IS                       | 13                            | 51  | M      | 10.52                    | 0                       |
| 14                                  | 35  | M      | 12.76                    | 0.80                     | 14                            | 52  | M      | 26.55                    | 0                       |
| 15                                  | 18  | M      | 13.01                    | 0                        | 15                            | 49  | M      | 23.01                    | 0                       |
| 16                                  | 29  | F      | 3.00                     | 0                        | 16                            | 52  | M      | 7.61                     | 0                       |
| 17                                  | 39  | M      | 17.65                    | 0                        | 17                            | 22  | M      | 20.16                    | 0                       |
| 18                                  | 35  | M      | 13.87                    | IS                       | 18                            | 20  | F      | 7.95                     | 0                       |
| 19                                  | 34  | M      | 20.02                    | 0                        | 19                            | 24  | M      | 6.16                     | IS                      |
| 20                                  | 49  | M      | 23.41                    | 0                        | 20                            | 21  | F      | 4.37                     | IS                      |
| 21                                  | 22  | M      | 70.00                    | 0                        | 21                            | 37  | F      | 3.97                     | 0                       |
| 22                                  | 21  | M      | 12.25                    | 2.42                     | 22                            | 27  | M      | 16.75                    | IS                      |
| 23                                  | 64  | F      | 3.00                     | 0                        | 23                            | 64  | F      | 23.22                    | 0                       |
| 24                                  | 33  | F      | 4.11                     | 0                        | 24                            | 41  | M      | 17.88                    | IS                      |
| 25                                  | 18  | F      | 5.13                     | 0                        | 25                            | 51  | F      | 8.85                     | IS                      |
| 26                                  | 29  | M      | 7.63                     | 2.90                     | 26                            | 37  | M      | 9.08                     | IS                      |
| 27                                  | 19  | F      | 6.18                     | 0                        | 27                            | 41  | F      | 3.37                     | IS                      |
| 28                                  | 33  | M      | 7.47                     | IS                       | 28                            | 34  | F      | 13.56                    | 0                       |
| 29                                  | 18  | F      | 6.89                     | 0                        | 29                            | 32  | F      | 8.26                     | 0                       |
| 30                                  | 18  | F      | 6.90                     | 0                        | 30                            | 22  | M      | 3.00                     | 0.2                     |
| 31                                  | 48  | M      | 10.01                    | 6.70                     | 31                            | 33  | F      | 6.15                     | IS                      |
| 32                                  | 32  | F      | 7.00                     | 0                        | 32                            | 26  | M      | 6.26                     | IS                      |
| 33                                  | 34  | K      | 35.00                    | 0                        | 33                            | 51  | F      | 4.64                     | 0                       |
| 34                                  | 34  | M      | 12.70                    | 0                        | 34                            | 24  | F      | 8.02                     | 0                       |
CD8-mediated gastrointestinal inflammation, indicating that expression of VDR is required to prevent replication of quiescent CD8+ T cells. The inability to signal through the VDR resulted in the generation of pathogenic CD8+ T cells from rapidly proliferating cells, which contributed to the development of inflammatory bowel disease (IBD) [15].

### Table 3 continued. Demographic and laboratory data in nasal poly patient and control groups.

| Nasal polyp group (n=46) (Patient No.) | Age | Gender | 25(OH)D VDR gene expression value | Control group (n=40) (Case No.) | Age | Gender | 25(OH)D VDR gene expression value |
|----------------------------------------|-----|--------|---------------------------------|---------------------------------|-----|--------|---------------------------------|
| 35                                     | 56  | M      | IS 8.89                         | 35                              | 21  | F      | IS 10.66                        |
| 36                                     | 25  | F      | IS 5.25                         | 36                              | 53  | M      | IS 8.40                         |
| 37                                     | 50  | M      | IS 6.46                         | 37                              | 20  | M      | IS 4.20                         |
| 38                                     | 42  | M      | IS 7.71                         | 38                              | 60  | M      | IS 15.46                        |
| 39                                     | 34  | M      | IS 8.50                         | 39                              | 52  | M      | IS 13.52                        |
| 40                                     | 35  | M      | IS 11.67                        | 40                              | 46  | F      | IS 5.20                         |
| 41                                     | 24  | F      | IS 6.84                         |                                  |     |        |                                 |
| 42                                     | 48  | M      | IS 35.00                        |                                  |     |        |                                 |
| 43                                     | 22  | M      | IS 19.87                        |                                  |     |        |                                 |
| 44                                     | 36  | M      | IS 4.81                         |                                  |     |        |                                 |
| 45                                     | 27  | M      | IS 8.25                         |                                  |     |        |                                 |
| 46                                     | 34  | M      | IS 17.35                        |                                  |     |        |                                 |

IS – insufficient sample; M – Male; F – Female; 25(OH)D – 25 (OH)Vitamin D; VDR – Vitamin D Receptor.

### Table 4. Comparison of nasal poly patient and control groups in terms of the presence of vitamin D receptor gene expression.

| VDR gene expression | Control (n=30) (n, %) | Nasal poly (n=40) (n, %) |
|---------------------|-----------------------|--------------------------|
| Yes                 | 1 (3.3%)              | 7 (17.5%)                |
| No                  | 29 (96.7%)            | 33 (82.5%)               |

χ² = 3.339; p = 0.065

Likelihood ratio χ² = 3.887; p = 0.049*

VDR – Vitamin D receptor. *

As because the possible decrease by the power of “Chi-square (χ²)” testing due to the expectation for the value of frequency of VDR positivity was lower than 5; the “P” value by the “likelihood ratio” test was considered instead.

### Table 5. The relation of the presence of vitamin D receptor gene expression with age, gender, and serum 25(OH)D levels.

| VDR gene expression | Yes (n=8) | No (n=62) | p     |
|---------------------|-----------|-----------|-------|
| Mean age ±SD        | 32.88±13.44 | 35.08±13.17 | 0.658 |
| Male/Female         | 7/1       | 38/24     | 0.145 |
| 25(OH)D (ng/ml) ±SD | 9.54±4.64 | 12.80±12.53 | 0.472 |
| 95 CI for 25(OH)D    | ±3.22     | ±3.12     | –     |
| Range for the true population mean | 6.32–12.76 | 9.68–15.92 | –     |

25(OH)D – 25 (OH) vitamin D; SD – standart deviation; CI – confidence interval.
In view of the results in our study, we think that levels of VDR gene expression may play a role in the etiology of NP. Our study is the first to investigate VDR gene expression in NP. Analysis with RT-PCR showed the presence of VDR gene expression in 7 cases in the NP group and in 1 case in the control group. The rate of VDR gene expression-positive cases was significantly higher in the NP group than in the control group (17% and 3.3%, respectively; likelihood ratio $\chi^2=3.887$; $p=0.049$). This situation may be due to increased VDR gene expression caused by inflammation in the NP tissue because the vitamin D-VDR signal inhibits mucosal inflammation by regulating the immune system [38,39]. The absence of gene expression in 33 cases in the NP group may be due to incomplete chronic inflammatory process because a certain time span is required to increase and attain certain levels of the gene expression related to inflammation [40–44]. Presence of gene expression in 1 case in the control group might have been due to an overlooked chronic inflammatory or allergic condition.

Conclusions

We found significantly higher levels of VDR gene expression in the NP group than in the control group. The increase in VDR gene expression may be a response to chronic inflammation in the NP tissue, or it may play a role in the etiopathogenesis of NP. To fully elucidate the role of vitamin D-VDR signal in the etiopathogenesis of NP, further studies on VDR gene expression are needed. Such studies would importantly contribute to the diagnosis and therapy of NP.

Conflict of interest

There is no conflict of interest.

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