Expression of Discoidin Domain Receptor 1 and Collagen Type IV Alpha in Nasal Polyposis

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Abstract

Background and Aim: There are various studies on the inflammatory pathogenesis of nasal polyposis (NP). It has been suggested that discoidin domain receptor-1 (DDR1) and collagen type 4A (COL4A) have a role in formation of inflammatory responses in the tissue microenvironment. The aim of the study was to study the expressions of DDR1 and COL4A in NP, and nasal mucosa.

Materials and Methods: This randomized, prospective, controlled clinical study was conducted on 17 patients' NP tissue and 24 subjects' inferior nasal turbinate. DDR1 and COL4A expressions were determined by quantitative real-time PCR. Histopathologic examinations were also carried out. Protein levels of the samples were determined using ELISA. The associations between the parameters were explored.

Results: DDR1 and COL4A transcripts were found at similar levels in all of the samples. There were correlations between DDR1 and COL4A mRNA levels in both the NP and control groups. There was also a negative correlation between extracellular edema and COL4A protein levels in NP.

Conclusion: To our knowledge, this is the first study to report DDR1 expression in NP tissue. We did not find any significant differences between NP and inferior nasal turbinate in terms of expressions of DDR1 and COL4A. Prospective studies with large populations should be planned for understanding DDR1 role in NP.

Keywords: Inflammation, DDR1, nasal polyp

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INTRODUCTION

Chronic rhinosinusitis is a chronic inflammatory pathology of the mucosa of the nose and paranasal sinuses. Nasal polyposis (NP) is considered a subgroup of chronic rhinosinusitis, featured by abnormal remodeling and persistent inflammation of sinonasal mucosa.[1] It has a quite changeable clinical progress frequently associated with aspirin intolerance, asthma attacks, and other circumstances. The etiology and the pathophysiology of NP are still subject to debate. Recent studies point to underlying genetic predispositions and environmental factors.[2] It is a multifactorial disease, but chronic inflammation is considered as an important factor in the pathophysiology of NP. Although tissue of NP is composed of mixed inflammatory cells, it is mainly featured by eosinophilic inflammation and T helper cell type-2 (Th-2) responses.[3] It has been suggested that NP and asthma have similar inflammatory process as Th-2-related inflammation characterized that infiltration with eosinophils.[4] Medical treatment is usually unsatisfactory, so that recurrences need repeated surgical interventions. Therefore, studies on the pathogenesis of NP have been continuing to this day—especially genetic studies focusing on inflammation.[2]

Discoidin domain receptors (DDRs) are one of the popular receptors in the study of inflammatory process such as asthma. DDR1–DDR2 receptors are type of receptor tyrosine kinases (RTKs). RTKs are functioned by several types of collagen and control cell metabolism.[5] Collagen is one of the most important and major extracellular matrix (ECM) components. The DDRs and nonintegrin collagen receptors are expressed widely in our tissues. There are 28 different types of collagens, which have structural and signaling roles via cell surface receptors. DDR1 receptor is also activated by collagens I-IV and also VIII.[6,7] Gene of DDR1 is situated on 6p21.3. It is composed of 17 exons and has five

isoforms.[8] DDR1 receptors are usually expressed in the epithelial cells of the gastrointestinal tract, lung, kidney, and mammary gland. They play important roles in embryo development and in human diseases such as cancer, inflammation, atherosclerosis, fibrosis, and arthritis.[9]

Dysregulation of ECM-induced signaling disrupts normal tissue organization.[10] DDRs have been found related to wound repair, proliferation, extracellular matrix remodeling, and migration.[9,11] It is known that there is remodeling process in the NP developing.[12] Histopathology of NP is similar to asthmatic airways displaying signs of proliferation of glands and epithelial layer, basal membrane thickening, edema, fibrosis, and stromal layer infiltration by cells.[4,10] DDR1 especially binds basement membrane collagen (collagen IV-most important structural component of basement membranes) in its native conformation.[6,7] Collagen IV provides a mechanical stability and is also an important in cell adhesion, survival, migration, proliferation, and differentiation of cells.[13]

Some authors suggested that there might be no direct relation between remodeling and inflammation in upper airway disease.[12,14] Studies also show that DDR1 and DDR2 are important in the expression of proinflammatory and profibrotic factors.[6,11] It has been demonstrated that when DDR1 is activated, production of chemokines is upregulated in an NF-κB-dependent way. It was, therefore, suggested that DDR1 has a role for inflammatory responses in the microenvironment of the tissue.[15] Additionally, it was also determined that DDR1 saves pulmonary fibroblasts from apoptosis.[16]

These findings have led us to hypothesize that DDR1 and collagen type IV alpha (COL4A) might contribute to the prolonged survival of eosinophils, inflammation, and basal membrane changings in NP. There are no studies in the literature exploring the association among NP, DDR1, and COL4A expressions.

METHODS

A prospective, randomized, controlled clinical study was designed and performed at the Departments of Otolaryngology, Pathology, and Medical Biology of Baskent University in Ankara, Turkey. This study was approved by Baskent University Institutional Review Board and Ethics Committee (project no: KA13/130) and supported by the Baskent University Research Fund. Written informed consents were obtained from all participating subjects.

This study included 17 patients diagnosed with NP. Diagnosis of NP was established based on each patient's medical history and on the results of nasal endoscopy and computerized tomography assessments. Endoscopic sinus surgery was applied to the patients over 18 years of age who had complaints of NP despite receiving medical therapy for at least 1 month. The control group consisted of 24 healthy subjects who underwent inferior turbinate excision due to a diagnosis of turbinate hypertrophy. Subjects with a history of using steroids in last month or of immune deficiency, diabetes mellitus, ciliary dysfunction, and cystic fibrosis were excluded from the study.

The tissue samples obtained from NP and inferior turbinate were examined at the Pathology and Medical Biology departments.

Histopathologic Examination

The paraffin embedded blocks were prepared from specimens of NP and inferior nasal turbinate. These tissues were painted with hematoxylin–eosin (H&E) and examined under light microscope. The tissues were assessed in terms of eosinophil counts, inflammation, and extracellular edema. A blind pathologist scored the inflammation and extracellular edema between 1 and 3 in H&E-stained sections. Nasal polyps were scored for eosinophilia based upon the number of eosinophils in H&E-stained sections. Sections were examined under 400× magnification in a blinded fashion, and positive cells were counted in 10 random sections for each sample, with the final number being the average number of cells per 10 high-powered fields (hpfs).

RNA Isolation and Reverse Transcription

Total RNA was extracted using Trizol reagent (TriPure isolation reagent, Roche, Mannheim Germany). cDNA was synthesized using commercially available kit (Transcriptor High Fidelity cDNA synthesis kit, Roche). The quality and quantity of RNA and cDNA were determined by spectrophotometrically.

Quantitative Real-Time PCR

DDR1 and COL4A expressions were determined by quantitative (Q) real-time PCR (LightCycler 2.0, Roche). Sybrgreen was used as fluorescent dye (Lightcycler Faststart DNA master sybr green, Roche). The primers for DDR1,[17] COL4A,[18] and internal control GAPDH[19] were as follows:

F 5′-AGATGCTGACATGAAGGGACA-3′ and R 5′-GGCAGTGGAATCTGACCAGG-3′ for DDR1;
F 5′-TGGTGCTACTTCTTCTTCTTTTT-3′ and R 5′- GCTTATCGCTGTCTTTTTCTCCT-3′ for COL4A; and
F 5′- AAGCTCATTTCCTGGTATGACA-3′ and R 5′- TCTTACTCCTTGGAGGCCATGT-3′ for GAPDH.

The Q real-time PCR reactions were performed in 20 μL volumes. The PCR mixtures consisted 0.5 μL of SYBR green, 5 ng of cDNA template, and 1.0 μL forward and reverse primers (10 μM). Annealing temperature was 61°C for all primers. For quantitative accuracy, each sample was run in triplicate. The threshold cycle numbers (Ct) were averaged, and the results were calculated using the $2^{\Delta\Delta Ct}$ method.

DDR1 and COL4A Levels

Tissue samples were rinsed in ice-cold PBS before homogenization and minced to small pieces by using scalpel. Homogenization was performed in a glass homogenizer on ice with a certain amount of PBS. Homogenates were centrifuged at 1,800 × g for 5 minutes at 4°C. Protein concentrations of samples were determined using the Bradford method. Protein levels of DDR1 and COL4A were determined by using commercially available ELISA kit according to the manufacturer's recommendations (Mybiorsource, CA, USA).

Statistical Analysis

Calculations were performed using the Statistical Package for the Social Sciences (SPSS) version 17.0 (IBM SPSS Corp.; Armonk, NY, USA) statistical software. RNA and protein levels of the tissues were compared with the Mann–Whitney and Wilcoxon W tests. Pearson chi-squared test was used to evaluate the association of eosinophil counts, inflammation, and extracellular edema with RNA and protein amounts of tissues. The values were expressed as mean score ± standard deviation (SD). A P value less than .05 was accepted as statistically significant.

RESULTS

The NP group consisted of 13 men and four women (mean age, 38.08 ± 10.6 years; range, 23-58 years). The control group consisted of 16 men and eight women (mean age, 39.18 ± 11.2 years; range, 25-65 years). The age ($P = .753$) and gender ($P = .729$) of the patients and controls did not differ significantly between the groups.

At the baseline, DDR1 and COL4A were expressed in the NP and inferior nasal turbinate as evidenced by real-time q-PCR and ELISA assay. Mean ± SD of the values was shown in Table 1.

Table 1. DDR1 and COL4A Expressions and Protein Levels

Groups (mean ± SD)	DDR1 protein (ng μL^{-1})	DDR1 mRNA (levels fold change)	COL4A protein (ng μL^{-1})	COL4A mRNA levels (fold change)
Patients with NP*	4.23 ± 2.26	0.002 ± 0.006	0.87 ± 0.17	0.00059 ± 0.00166
Inferior nasal turbinate (control group)	6.05 ± 3.83	0.003 ± 0.008	0.84 ± 0.14	0.001173 ± 0.003084
P value	0.27	0.751	0.624	0.743
Z value	−2.210	−.318	−.490	−.328

*NP: nasal polyposis.

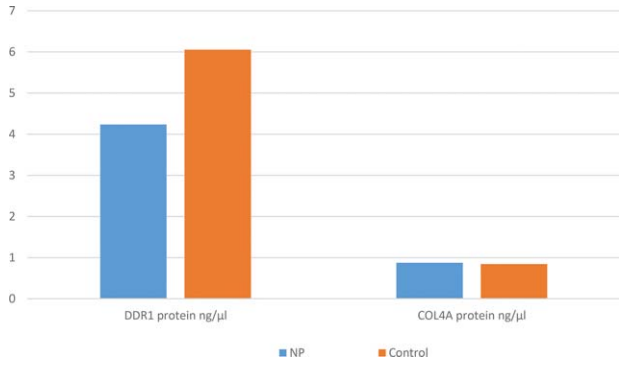

Figure 1. DDR1 and COL4A protein levels.

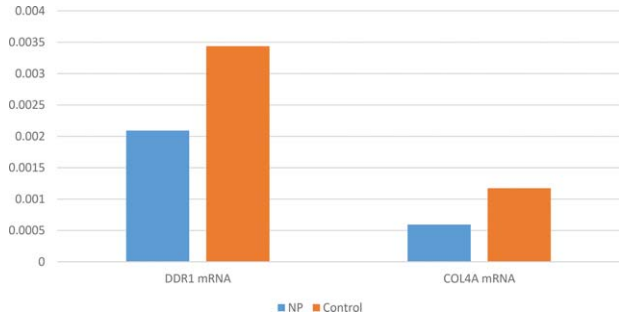

Figure 2. DDR1 and COL4A mRNA levels (fold change).

By using real-time Q-PCR, DDR1 transcripts were found to be expressed at similar levels in all samples tested in NP and inferior nasal turbinates. In accordance with the DDR1 expression, protein amounts measured by ELISA assay were found at similar in all samples tested in NP and inferior nasal turbinates (Figures 1 and 2).

COL4A mRNA expression was similar between NP group and inferior nasal turbinate group. In accordance with the COL4A expression, protein amounts of COL4A measured by ELISA assay were found similar levels in all samples in two groups (Figures 1 and 2).

There was a correlation between DDR1 and COL4A mRNA levels in both NP and control groups (r: 0.990, $P < .001$; r: 0.947, $P < .001$, respectively).

Table 2. Histopathologic Examination Findings Scoring

		NP tissue
	Mean ± SD	37.06 ± 34.734
Eosinophil	Minimum-maximum	5-90
Extracellular edema	Median	2
	Minimum-maximum	1-3
Inflammation	Median	1
	Minimum-maximum	1-3

Mean ± SD values concerning the histopathologic examination of the NP tissues are shown in Table 2. Evaluation of the relationships among DDR1 expression, COL4A expression, protein levels of DDR1, protein levels of COL4A, and histopathologic parameters such as eosinophil counts and inflammation revealed no statistically significant differences. However, there was a negative correlation between extracellular edema and COL4A protein levels in NP (Table 3).

DISCUSSION

The etiology and pathophysiology of NP have not yet been fully elucidated. For this reason, NP is the subject of many studies, and especially molecular genetic studies, investigating its pathophysiology. This is the first study to investigate the expressions of DDR1 and COL4A in NP using the real-time Q-PCR, to the best of our knowledge. We compared the expression and protein levels of DDR1 and COL4A in the NP and control mucosa with the levels in the inferior nasal turbinate. We demonstrated that both control mucosa and NP expressed DDR1 and COL4A. There were no significant differences between the NP and control groups in terms of DDR1 and COL4A expression and protein levels. However, DDR1 and COL4A mRNA levels were in correlation in both the NP and control group. Comparison of the histopathologic parameters of NP (eosinophil and inflammation) with DDR1 and COL4A expression revealed no statistically significant correlations between the parameters. However, a negative correlation was observed between extracellular edema and COL4A protein levels.

Thickening of basement membrane, epithelial damage, and tissue eosinophilia are histopathologic features of both asthma and NP.[20,21] Ponikau et al.[21] demonstrated the airway remodeling through epithelial sloughing and basement membrane thickening, while eosinophilic infiltration was both seen in patients with asthma and chronic rhinosinusitis. Nonaka et al.[22] also showed that infiltration of eosinophils was related to

Table 3. Association among Histopathologic Parameters and DDR1, COL4A Protein, and mRNA Levels in NP Tissue

		Eosinophil	Extracellular edema	Inflammation
DDR 1 protein (ng μL^{-1})	r	0.025	0.025	0.104
	P	.924	.924	.693
DDR1 mRNA levels (fold change)	r	–0.058	0.058	–0.337
	P	.925	.958	.186
COL4A protein (ng μL^{-1})	r	–0.090	–0.595	–0.328
	P	.732	.012	.257
COL4A mRNA levels (fold change)	r	–0.219	–0.219	–0.301
	P	.415	.415	.257

structural abnormalities such as basement membrane thickening and fibrosis. Saitoh et al.[23] described that basement membrane thickness and epithelial damage in chronic rhinosinusitis with NP were significantly more than in the control group. They showed that these changes were correlated with amount of eosinophils in the epithelial and subepithelial layers. They also suggested that infiltrated eosinophils in the epithelial and subepithelial layers play a role in the mucosal remodeling of NP.[23]

The DDR1 expression was also demonstrated in the bronchial epithelium.[24] Roberts et al.[24] suggested that DDR1 has a regulatory role by communicating between airway extracellular matrix and bronchial epithelium. Based on the one airway hypothesis, we aimed to investigate DDR1's role in the pathophysiology of NP in the lung. Within the scope of our study, we demonstrated the expression of DDR1 in NP and inferior nasal turbinate mucosa. However, the expression level and protein level of DDR1 were same in both groups. In agreement with our study findings, Chua et al.[25] showed that DDR1 was equally expressed in lymphoid hyperplasia specimen, nasal epithelial cells, nasopharyngeal carcinoma, NPC meta, and other head and neck tumors tested by real-time Q-PCR.

We also investigated the correlation among histopathologic parameters, DDR1, and COL4A expression and protein levels. Concerning the histopathologic parameters, we only identified a negative correlation between extracellular edema and COL4A protein levels. In addition, DDR1 and COL4A expressions and protein levels were—as expected—correlated in both the NP and control groups. It is not clear whether the amount of total collagen rises or decreases. Also, there are currently no studies exploring the expression of collagen types in NP. Meng et al.[12] demonstrated by using the picrosirius red staining method that there was a lack of total collagen in the early stage polyps compared to middle nasal turbinate. Van Bruaene et al.[26] also demonstrated that the total collagen amount in the ECM was significantly lower in NP compared to the controls. In contrast, Molet et al.[27] showed by using the immunohistochemistry method that compared with normal control nasal turbinate tissues, collagen types I, III, and V were present at increased levels in the submucosal connective tissue and in the basement membrane zone of NP tissues.

It is known that NP tissue is generally surrounded with pseudostratified ciliary epithelia. NP tissue is distinguished from normal nasal mucosa by the presence of stromal edema, eosinophilic inflammation in subepithelial region, secretory hyperplasia, and epithelial cell proliferation. Cell infiltration in NP tissue comprises neutrophils, lymphocytes, macrophages, plasma cells, eosinophils, and mast cells. In NP, eosinophils are mostly seen in inflammatory cells.[4,10] However, both the presence and level of eosinophilia in NP can be quite variable.[28] Payne et al.[29] suggested that idiopathic NP can be distinguished as eosinophilic or noneosinophilic NP. They demonstrated that noneosinophilic NP tissues have glandular hypertrophy, dense collagen deposition, mononuclear cellular infiltrate, and increased fibrosis. In contrast, eosinophilic NP displays edema, rare glandularity, and minimal collagen deposition except within the basement membrane. It possible to state that due to the different etiologies and histopathologic futures of NP, we were not able to observe in NP any differences in the expressions of DDR1 and collagen.

In conclusion, although this study provided preliminary results indicating the expression of DDR1 in NP tissue, we could not show any differences between the NP and control groups. This can be attributed to the number of patients in the NP and control groups. However, to our knowledge, this is the first study exploring the role of DDR1 in NP. While DDRs play an important role in the relevant physiological and pathological processes, a detailed understanding of the underlying molecular mechanisms is currently lacking. Understanding these mechanisms is important for developing selective DDR inhibitors. For this reason, it is necessary to plan and conduct prospective studies with larger populations that would provide a better understanding of DDR1's role in NP.

Ethics Committee Approval: Ethical committee approval was received from the Baskent University (project no: KA13/130).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.T.B, S.S.E, E.Y; Design - S.T.B, S.S.E, E.Y.; Supervision - S.S.E., E.Y, H.Ö; Resource - S.S.E., S.T.B. H.A., A.O.K; Materials - S.S.E., S.T.B. H.A., A.O.K; Data Collection and/or Processing - S.S.E., S.T.B. H.A., A.O.K, Y.K., E:Y., H.Ö; Analysis and/or Interpretation - S.S.E., S.T.B. H.A., A.O.K, Y.K., E:Y., H.Ö; Literature Search - S.T.B., S:S:E., E.Y., A.O.K., H.A., H.O.; Writing - S.T:B.; Critical Reviews - S.S.E., E.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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