

Goblet Cell Density of the Inferior Turbinates in Patients with Perennial Allergic and Nonallergic Rhinitis

Gilead Berger, M.D., Zvi Marom, M.D.,* and Dov Ophir, M.D.

ABSTRACT

Nasal mucus production is regulated by submucosal glands and epithelial goblet cells. The role and especially the number of the latter are quite debatable. The present study compares the distribution and density of goblet cells in the inferior turbinates of patients with perennial allergic and nonallergic rhinitis to normal controls. The periodic acid Schiff-alcian blue whole-mount method was used to identify and count their number. Goblet cell distribution was found nonhomogeneous, and considerable variations were observed among adjacent localities of the same specimen. The mean number of goblet cells per mm² was 6499 in normal controls (n = 12), 6818 in patients with perennial allergic rhinitis (n = 13), and 6801 in patients with perennial nonallergic rhinitis (n = 18). Statistical analysis confirmed that the density of goblet cells did not differ significantly between patients with and without allergy, as well as between each group of patients and controls. Therefore, it could be concluded that the number of goblet cells in the inferior turbinate is not influenced by the presence of pe-

rennial allergic or nonallergic rhinitis. (American Journal of Rhinology 11, 233–236, 1997)

The mucosal lining of the nose is endowed with a mucociliary transportation system that constitutes the first line of defense, protecting the lungs from particles, microorganisms, and chemical irritants. The system consists of ciliated respiratory epithelium and mucus-producing elements. In order to maintain its homeostasis, a proper production and secretion of mucus from submucosal glands and epithelial goblet cells is necessary.

Mogensen and Tos^{1,2} reported on the density of goblet cells in the normal adult nasal septum and turbinates; they also described changes in the distribution and density of goblet cells in the nasal mucosa of patients with nasal polyposis³ and Kartagener's syndrome.⁴

The present study forms part of a basic research on the pathology of perennial rhinitis. The latter refers to the clinical condition in which rhinorrhea and/or nasal blockage occur throughout the year and are not limited to seasonal exacerbations. A significant proportion of the patients with perennial rhinitis manifests on physical examination hypertrophy of the inferior turbinates, which blocks the nasal passages. Classification of this heterogeneous population often differentiates between patients with and without allergy. The laboratory diagnosis of allergic disease is usually based on the detection of allergen-specific IgE antibodies in the skin and/or the patient's serum by cutaneous prick tests and RAST, respectively.

Numerous studies deal with the role of mast cells, basophils, and eosinophils in allergic diseases of the nose, but only few discuss the contribution of goblet cells to the

*From the Departments of Otolaryngology-Head and Neck Surgery and *Pulmonary Medicine, Meir General Hospital, Kfar Saba, Sackler School of Medicine, Tel-Aviv University, Israel. Supported by a grant from the Dr. Herman Schauder Memorial Endowment Fund, Sackler School of Medicine, Tel-Aviv University.*

Address correspondence and reprint requests to Dr. Gilead Berger, Department of Otolaryngology-Head and Neck Surgery, Meir General Hospital, Kfar Saba, Israel 44281.

underlying pathophysiology of the nasal mucous membranes in patients with perennial allergic and nonallergic rhinitis. Toppozada and Tallat⁵ found increased numbers of goblet cells in chronic allergic rhinitis. Their conclusions, qualitative by nature, were based on examination of tiny pieces of nasal epithelium by electron microscopy. Mygind et al.⁶ in a semiquantitative study found a significant increase of goblet cells in chronic rhinitis. Larsen et al.⁷ performed a quantitative study by using the whole mount method and found that the number of goblet cells in the inferior turbinates of patients with chronic rhinitis does not differ significantly from that of normal ones. In light of the insufficient and conflicting data, the present study was undertaken to provide quantitative information regarding the number and distribution of goblet cells in the inferior turbinates of patients with perennial allergic and nonallergic rhinitis compared with normal controls.

MATERIAL AND METHODS

The material consisted of hypertrophic inferior turbinates removed from 31 patients with perennial rhinitis who failed to respond to medical treatment and who underwent bilateral inferior turbinectomy (Ophir et al.⁸). Thirteen patients were allergic to house dust mite, and the remaining 18 had negative prick skin tests with 20 common airborne allergens. None of them received topical or systemic corticosteroids during the month before surgery.

Twelve patients admitted for septoplasty due to unilateral nasal obstruction served as controls. On examination, their inferior turbinates appeared normal with no symptoms or further signs of nasal disease. They underwent allergic assessment, and all had negative prick skin tests with 20 common airborne allergens. Biopsies were taken from the middle part of the inferior turbinates on the unobstructed side of the nasal chamber.

Each specimen was divided into two. One portion was fixed in buffered formaldehyde, processed in the usual manner, and embedded in paraffin. Two sections of each specimen, 5 μ m thick, were cut in a plane perpendicular to the mucosal surface. One section was stained with hematoxylin and eosin to study the histology, and the second was stained with PAS (Periodic Acid Schiff) to demonstrate mucus within epithelial goblet cells and submucosal glands. The other portion was immediately transferred into formal-alcohol solution for fixation. Following fixation, the entire mucosa was fine dissected under the operating microscope, removing the deeper layer of the lamina propria, which included submucosal glands and the vascular plexus, and leaving the epithelium with the basement membrane and a superficial layer of the lamina propria without neighboring glands or capillaries. The mucosa was stained with the PAS-alcian blue whole mount method⁷ and cleared with anise oil, which makes the goblet cells stand out intensely blue on a pale blue background. The mucosa was mounted on a glass slide, immersed in an anise oil-colophonium

mixture, and a coverslip was applied and sealed with paraffin.

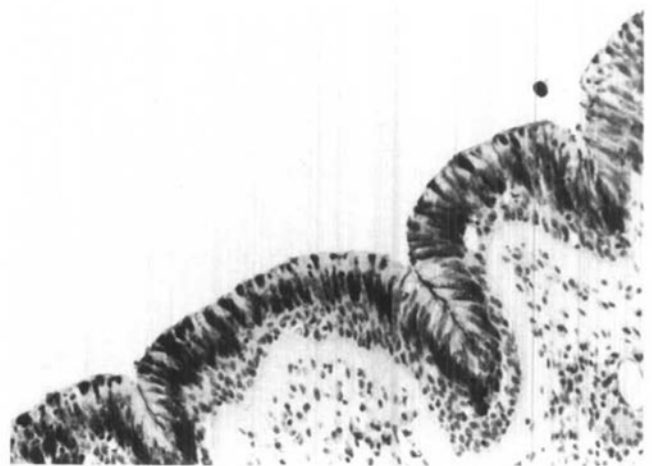
Since the number of goblet cells varied considerably between the anterior and posterior portions of the inferior turbinate, as well as between its medial and lateral walls, measurements were taken at a reference point in the medial wall of the middle third of the inferior turbinate. The specimens were studied with a calibrated eyepiece light microscope at a magnification of 200. Ten areas of 0.16 mm² were counted in each specimen, and results were expressed as a mean number of goblet cells per mm².

Statistical analysis was performed by the one-way analysis of variance.

RESULTS

The hematoxylin-eosin and the PAS stained sections at the medial wall of the middle third of the inferior turbinate in patients with perennial allergic and nonallergic rhinitis as well as controls, demonstrated pseudostratified ciliated columnar epithelium exclusively. Neither transitional nor squamous cell epithelium were encountered in any of the sections. Many goblet cells, filled with mucus, were scattered unevenly among the ciliated cylindric epithelial cells (Fig. 1).

In the whole mount specimens, goblet cells were shaped round to oval, sharply defined, and appeared as blue patches on a pale blue background. Their size varied considerably, depending upon their phase in the secretory cycle, ranging mostly between 5–10 μ m in diameter. Many of the goblet cells were isolated, but some were seen in pairs or in clusters of several cells (Fig. 2). Their distribution was not homogeneous, and considerable variations in goblet cell density were observed between adjacent localities of the same specimen. Table I shows the mean number of goblet cells per square millimeter at the medial wall of the middle third of the inferior turbinate in patients with perennial



rhinitis. (PAS. original magnification $\times 100$)

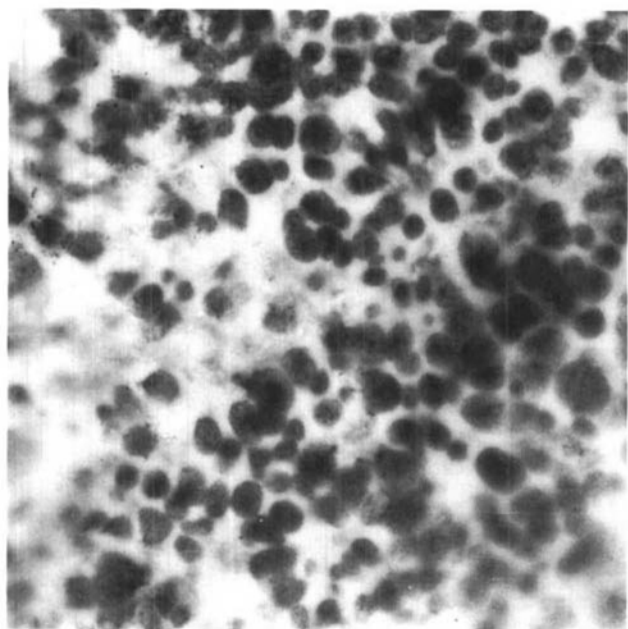


Figure 2. Whole mount specimen of a patient with perennial allergic rhinitis. Goblet cells appear isolated, in pairs and clusters. (PAS-alcian blue, original magnification $\times 100$)

TABLE I

Goblet Cell Count			
	No. of Patients	No. of Goblet Cells per mm ²	
		Range	Mean
Normal controls	12	4147–7843	6499 $\pm$ 1077
Perennial allergic rhinitis	13	5250–9234	6818 $\pm$ 1027
Perennial nonallergic rhinitis	18	5425–9375	6801 $\pm$ 1156

allergic and nonallergic rhinitis and in the controls. A comparison of goblet cell density revealed no significant difference between allergic or nonallergic patients ($p = .3442$), as well as between each group of patients and controls ($p = .4342$ and $p = .4157$, respectively).

DISCUSSION

Larsen et al.⁷ performed a quantitative study on the density of goblet cells in the inferior turbinates of patients with chronic hypertrophic rhinitis and did not find a statistically significant difference between the number of goblet cells in patients with and without rhinitis. The present study is based on a similar PAS-alcian blue whole mount method that enables accurate quantitative counts of the goblet cell population in the inferior turbinates of patients with perennial rhinitis. To the best of our knowledge, this is the first study to provide information regarding the number

of goblet cells in patients with perennial allergic rhinitis. The results indicate that perennial allergic and nonallergic rhinitis are not associated with an increase in the number of goblet cells at the medial wall of the middle third of the inferior turbinate and probably throughout the nasal mucosa, as their numbers did not differ significantly between patients with chronic rhinitis and controls.

It is worthy of note that the present observation is in accordance with the results of a previous histopathologic study⁹ that found a considerable resemblance between perennial allergic and nonallergic rhinitis with respect to the mucosal inflammation. In both ailments the inflammatory cell infiltration consisted mostly of lymphocytes and other mononuclear cells; eosinophils were present in moderate numbers and the number of mast cells was alike. In fact, diagnosis is dependent upon demonstration of IgE antibodies, since it is difficult to distinguish between the two diseases on the basis of morphologic appearance, or on clinical grounds.

Goblet cell population, in the nasal passages of normal subjects, varies considerably and an inverse ratio could be found between their number and the strength of the air current.^{1,2} Their number is abundant in regions where air current is scanty, and vice versa. Thus, it has been reported that more goblet cells are found on the inferior turbinate than on the middle one. Within the former, there are more goblet cells on the lateral wall than on its medial wall. The same applies to the inferior versus the superior aspect of the inferior turbinate. Likewise, the density of goblet cells is higher in the posterior portions of the nasal septum and the inferior turbinate than anteriorly. This rule is also applicable in animals, as Hilding,¹⁰ and Mogensen and Tos¹¹ occluded a nostril of a rabbit and later found an increase in the number of goblet cells in it. Another factor that influences the goblet cell density is the type of the epithelium. Their numbers are the highest in pseudostratified ciliated columnar epithelium, decreasing dramatically in transitional type epithelium, and almost disappearing in regions covered by squamous epithelium.¹²

It has been reported that several diseases are associated with significant changes in the number of goblet cells in the nose. Their number is markedly decreased in atrophic rhinitis,^{13,14} whereas chronic infections result in an increased goblet cell density.¹⁵ Although the mechanisms involving goblet cell hyperplasia are not fully established in humans, a causative relationship between neutrophil accumulation and induction of goblet cell hyperplasia is suggested in animal models. These studies demonstrated an increase in goblet cell number following instillation of supernatant from either lysed purified neutrophils or activated neutrophils into the trachea of hamsters or rats.^{16,17} It has also been suggested that goblet cell secretion adds little to the total volume of nasal fluid in normals, but rather contributes to the viscoelastic properties of the mucous blanket.¹⁸ Although the secretion of submucosal glands is controlled by the autonomic nervous system, goblet cells lack innervation

in humans, and the mechanism that regulates their secretory activity under normal conditions is unknown. Nevertheless, there is evidence to suggest that inhaled histamine in guinea pigs increases airway goblet cell secretion by stimulating histamine H₂-receptors on goblet cells and that intravenous histamine produces a similar effect through stimulation of histamine H₁-receptor-mediated release of acetylcholine from cholinergic nerve terminals.¹⁹ It was also found that other mediators of inflammation, such as PAF, induce goblet cell secretion under inflammatory conditions.²⁰ Likewise, preliminary studies have revealed that neutrophils as well as eosinophils contain mucus secretagogues that induce secretion from submucosal glands and goblet cells.^{21,22}

In conclusion, as goblet cell number does not increase in the inferior turbinates of patients with perennial allergic and nonallergic rhinitis, further data are needed to examine whether the amount and composition of goblet cell mucus secretion undergoes significant changes, and if so, to look into the possible mechanisms involved in these changes.

ACKNOWLEDGMENTS

Dr. Joelle Bernheim, Head of Department of Pathology, Meir Hospital, Kfar Saba, produced the illustrations. Dorit Lerman prepared the sections. Ilana Gelerenter, M.A., School of Mathematics, Tel-Aviv University, provided statistical assistance. Rachel Berger, B.A., edited the manuscript and Yael Ben-Shimol typed it.

REFERENCES

1. Mogensen C, Tos M. Density of goblet cells in the normal adult human nasal septum. *Anat Anz* 141:237-247, 1977.
2. Mogensen C, Tos M. Density of goblet cells on normal adult nasal turbinates. *Anat Anz* 142:322-330, 1977.
3. Tos M, Larsen PL, Moller K. Goblet cell density in nasal polyps. *Ann Otol Rhinol Laryngol* 99:310-315, 1990.
4. Mogensen C, Mygind N, Pedersen M. Quantitative estimation of goblet cell density of the nose in patients with Kartagener's syndrome (primary ciliary dyskinesia). *Eur J Respir Dis* 64 (suppl 128):464-465, 1983.
5. Topozada HH, Talaat MA. Human nasal epithelium and cellular elements in chronic allergic rhinitis. *J Otorhinolaryngol* 37:333-343, 1975.
6. Mygind N, Viner AS, Jackman N. Histology of nasal mucosa in normals and in patients with perennial rhinitis. *Rhinology* 12: 131-136, 1974.
7. Larsen PL, Tos M, Mogensen C. Nasal glands and goblet cells in chronic hypertrophic rhinitis. *Am J Otolaryngol* 7:28-33, 1986.
8. Ophir D, Schindel D, Halperin D, Marshak G. Long-term follow-up of the effectiveness and safety of inferior turbinectomy. *Plast Reconstr Surg* 90:980-984, 1992.
9. Berger G, Goldberg A, Ophir D. The inferior turbinate mast cell population of patients with perennial allergic and nonallergic rhinitis. *Am J Rhinol* 11:63-66, 1997.
10. Hilding A. Experimental surgery of the nose and sinuses. *Arch Otolaryngol Chicago* 16:9-18, 1932.
11. Mogensen C, Tos M. Experimental surgery of nose. I: Air-flow and goblet cell density. *Acta Otolaryngol (Stockh)* 86:289-297, 1978.
12. Larsen PL, Tos M. Nasal polyps: Epithelium and goblet cell density. *Laryngoscope* 99:1274-1280, 1989.
13. Holopainen E. Nasal mucous membrane in atrophic rhinitis with reference to symptom-free nasal mucosa. *Acta Otolaryngol suppl* 227:1-55, 1967.
14. Mygind N, Thomsen J, Balslev Jorgensen M. Ultrastructure of the epithelium in atrophic rhinitis: Scanning electron microscopic studies. *Acta Otolaryngol* 77:439-446, 1974.
15. Petruson B, Hanson H-A, Karlsson G. Structural and functional aspects of cells in the nasal mucociliary system. *Arch Otolaryngol* 110:576-581, 1984.
16. Snider GL, Lucey E, Christensen TG, et al. Emphysema and bronchial secretory cell metaplasia induced in hamsters by human neutrophil products. *Am Rev Respir Dis* 129:155-160, 1984.
17. Lundgren JD, Kaliner M, Logun C, Shelhamer JH. Dexamethasone reduces rat tracheal goblet cell hyperplasia produced by human neutrophil products. *Exp Lung Res* 14:853-863, 1988.
18. Mygind N, Brofeldt S, Ostberg B, et al. Upper respiratory tract secretions: Pathophysiology. *Eur J Respir Dis* 71, Suppl 153, 26-33, 1987.
19. Takeyama K, Tamaoki J, Nakata J, Konno K. Effect of oxitropium bromide on histamine-induced airway goblet cell secretion. *Am Respir Crit Care Med* 154:231-236, 1996.
20. Lellouch-Tubiana A, Lefort J, Simon M-T, et al. Eosinophil recruitment into guinea pig lungs after PAF-acether and allergen administration. *Am Rev Respir Dis* 137:948-954, 1988.
21. Logun C, Rieves RD, Lundgren JD, et al. Activated human neutrophils release a high molecular weight protein which stimulates respiratory glycoconjugate release from human airways *in vitro*. *Am Rev Respir Dis* 137:A14, 1988.
22. Lundgren JD, Davey RT, Rieves D, et al. The effect of eosinophil granule extract on airway respiratory glycoconjugate secretion *in vitro*. *Am Rev Respir Dis* 137:A11, 1988. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.