Mucin Expression in Nasal Polyps

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Core Messages

- As a part of the airway mucosa, nasal polyps express a wide range of mucin genes and proteins.
- Nasal polyps express the first nine mucin genes studied so far (MUCs1–4, 5AC, 5B and 6–8).
- More mucin genes are expected to be expressed in nasal polyps.
- The wide range of mucin expression patterns reflects a wide range of internal and external environmental factors involved in the development of nasal polyps.
- Mucin genes up-regulated in nasal polyps include MUC1, 2, 4, 5AC, 5B and 8.
- Sub-mucosal glands play a more important role in mucin expression than surface epithelium.
- Most of the studies on mucin expression in nasal polyps are focused on basic science.
- The role of steroids in modulating mucin gene expression in nasal polyps is still unclear.
- Further studies are needed to illustrate the role of different variables that control mucin expression in nasal polyps.
- The role of inflammatory mediators needs to be studied to help invent new treatment modalities.

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8.1 Introduction

Rhinorrhea with increased mucus secretion is one of the main symptoms related to nasal polyps. This can involve increase of quantity and/or change of quality of nasal mucus. This alteration of amount and/or physical properties of nasal mucus can have a deleterious effect on nasal mucociliary transport, which depends in part on the quantitative and qualitative properties of mucus secretion. In normal situation, the gel-like properties of airway mucus secretion depend solely on the presence of high molecular weight glycoproteins known as mucins in the mucus secretion. These are large molecules formed of sub-units joined end to end by disulphide bonds with a core protein to which hundreds of carbohydrate chains are O-linked [4]. Histochemical studies have shown that in the airway mucosa mucus-producing (goblet) cells of the surface epithelium and mucus and serous cells of the sub-mucosal glands produced different types of mucins [28].

8.2 Mucin Genes

To date 20 human mucin genes named MUC1, 2, 3A, 3B, 4, 5AC, 5B, 6–9, 11–13 and 15–20 have been identified by cDNA cloning. MUCs2, 5AC, 5B, 6, 8 and possibly 19 are secretory gel-forming mucins while MUCs1, 3A, 3B, 4, 11–13, 15–18 and 20 are membrane bound. MUC7 is a secretory, but not gel-forming mucin as it exists as a monomer. Secreted and membrane-bound forms of MUC9 have been identified. All the currently known human mucin genes, excluding MUCs 9, 11, 16 and 17, have been shown to be expressed by human airway mucosa [1]. As a part of the airway mucosa, nasal polyps are expected to express a wide spectrum of mucin genes comparable to that identified in the airway mucosa.

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8.3 Sources of Mucus Hyper-Secretion in Nasal Polyps

Increased nasal mucus secretion in the presence of nasal polyps can be due to one or more of the following reasons:

1. Sinus infection that occasionally coexists or complicates the presence of nasal polyps [1, 4, 31]. In a previous study, we found that at least three mucins, MUC2, MUC5AC and MUC5B, are expressed in sinus and mixed nasal mucus secretion of chronic sinusitis patients [2]. An inverse relation between MUC2 and MUC5AC mucin levels in sinus mucus secretion of these patients was noted. This inverse relation was significantly high only in the presence of nasal polyps [4].
2. Increased surface area of the functioning mucous membrane by polyp formation. Although there are areas of squamous metaplasia of respiratory mucosa covering the polyps, mucin expression has been identified in these squamous epithelia [3].
3. Increased number of mucus secretory elements (goblet cells and/or sub-mucosal gland). This has been reported in inflammatory airway diseases. Inflammatory mediators such as interleukin (IL)-9 and IL-13 up-regulate mucus expression by goblet cell hyperplasia in airway inflammation [25, 33, 49]. Increase of sub-mucosal gland area in inflamed sinus mucosa has also been reported [32].
4. Release of inflammatory mediators. Several inflammatory mediators can up-regulate specific mucin gene in inflamed airway mucosa. MUC2 expression is up-regulated by TNF-α [24, 40], interleukin (IL)-1β [23], IL-9 [25] and leukotriene (L) D4 [8, 42]. MUC4 expression is up-regulated by IL-1β, lipopolysaccharide [7] and IL-9 [15]. MUC5AC expression is up-regulated by neutrophil elastase [18], IL-1β [23], IL-4 [14], IL-6 [40], IL-9 [25, 33], LD4 [8] and TNF-α [40, 48]. However, the role of IL-4 on MUC5AC mRNA and MUC5AC mucin in cultured normal human nasal epithelial cells has been reported to be inhibitory rather than stimulatory [37]. MUC5B expression is up-regulated by IL-6 and TNF-α [40]. MUC8 expression is up-regulated by TNF-α and IL-1β [21, 41, 47] and prostaglandin E2 [12]. The release of one or more of these inflammatory mediators would result in increased activity (hyper-functioning) of the secretory elements of the airway mucosa. Altered quantity (mucin up-regulation) and/or quality (different mucin expression) would disturb mucociliary transport and result in the clinical manifestation of anterior and posterior rhinorrhea commonly complained of by polyp patients.

8.4 Studies of Mucin Gene Expression in Nasal Polyps

8.4.1 Techniques

Several techniques have been employed to study mucin gene expression in nasal polyps. Of these, in situ hybridization [3, 11, 27] is a sensitive qualitative technique to study mucin gene expression at the level of mRNA. Using oligonucleotide probes to the tandem repeat sequence in the mucin gene under investigation provides signal amplification and enhancement by hybridising maximum number of probes along the tandem repeat units in the same mRNA molecule. As it is applied on histological sections, in situ hybridization has the advantage of facilitating cellular localization of expressed mucin genes. However, as signal intensity does not depend on the number mucin mRNA molecules but on the number of tandem repeat units in the mRNA molecules, this technique of in situ hybridization cannot be considered as a quantitative test for mucin gene expression. It can only give semi-quantitative assessment of the level of mucin gene expression. Other techniques of mucin gene study include reverse transcriptase-polymerase chain reaction (RT-PCR) [16]. Mucin protein studying techniques include enzyme linked immunosorbent assays (ELISA) [7], Western blots [48] and immunohistochemistry [11, 27].

8.4.2 Control Mucosa for Mucin Gene Studies in Nasal Polyps

Different sources of healthy nasal mucosa have been used as a control mucosa for mucin gene expression studies in nasal polyps. Inferior turbinate mucosa is easy to harvest [10, 22, 37]. However, Mogensen and Tos [29] have reported that goblet cell density increases from anterior to posterior along the inferior turbinates. Furthermore, considering the physiological functions of the inferior turbinates, it is not clear if this mucosa can

present an ideal control model for mucin gene expression in nasal polyps. Healthy posterior ethmoid mucosa was utilised [20] as it represents a part of the mucosal lining the ethmoid sinuses from which nasal polyps usually arise and which is commonly involved in the chronic sinus infection. It is relatively easy to harvest posterior ethmoid mucosa after the removal of nasal polyps with anterior ethmoid mucosa. Due to anatomical and physiological reasons, this mucosa seems more suitable than inferior turbinate mucosa as a control for mucin gene expression study in nasal polyps. Sphenoid sinus mucosa was used as a control as it is embryologically a part of the posterior ethmoid with the advantage of being further away from anterior ethmoid sinuses, and therefore, is relatively less likely to be involved in ethmoid sinus pathology than the posterior ethmoids. The epithelium of the ethmoid and sphenoid sinus mucosa (similar to that of inferior turbinates) is typical of the respiratory epithelium (pseudostratified ciliated columnar epithelium with goblet cells). The sub-mucosal layer is usually thin with a few glandular elements.

8.4.3 Main Studies

There are three main studies that investigated the expression of a wide range of mucin genes in nasal polyps with a control nasal mucosa [3, 22, 27]. The first study used inferior turbinate mucosa as a control and the second one used sphenoid sinus mucosa. The third study did not define the source of control (normal) nasal mucosa. On the basis of the study of Reid et al. [34] on the developmental expression of mucin genes in human airways, which showed no expression of MUC3, 6 or 8 in human foetal airways, Kim et al. [22] excluded MUC3 and 6 from their study, which investigated the expression of the first nine mucin genes (MUCs1, 2, 4, 5AC, 5B, 7 and 8) in nasal polyp epithelium. They used pooled cell scrapings from normal inferior turbinate mucosa as a control epithelium employing RT-PCR and immunoblotting. They found that all the mucin genes they studied are expressed at various levels in normal inferior turbinate epithelium. Mucin expression in the sub-mucosal gland was not investigated.

We studied mucin gene expression in healthy sphenoid sinus mucosa as a control for nasal polyps. Healthy sphenoid sinus mucosa expressed MUCs1–4, 5AC and 5B, but not MUC6 or 7. The expression was mainly epithelial. Mucin gene expression in sphenoid sinus mucosa was mainly of membrane-bound mucins (MUC4 and 3), which were expressed in most of the samples [3]. In sub-mucosal gland, mucin expression was infrequent and MUCs4 and 5B expression was generally weak, while that of MUC5AC was moderate. No MUC1, 2 or 3 expression was detected in the sub-mucosal gland of healthy sphenoid sinus mucosa. Martínez-Antón et al. [27] employed in situ hybridization to study MUC2, 4, 5AC and 6 mRNA expressions in *healthy inferior turbinate mucosa* and nasal polyps. They also used immunohistochemistry to study MUC1, 2, 4–8 mucin protein expression. They found that MUC1, MUC4 and MUC5AC mucins are highly expressed in the epithelium of normal nasal mucosa. MUC8 was highly detected at both the epithelium and sub-mucosal glands while MUC5B was mainly detected in the sub-mucosal glands. MUC6 and MUC7 were scarcely expressed in normal nasal mucosa with MUC7 restricted to the sub-mucosal glands. There are other studies that investigated the expression of one or a few mucin genes in nasal polyps [8, 10, 12, 16, 20, 41].

8.5 Mucin Gene Expression in Nasal Polyps

Histologically, nasal polyps are inflammatory polyps covered by respiratory epithelium with areas of squamous metaplasia and focal thickening of sub-epithelial basement membrane. The sub-mucosal glands are occasionally dilated and lined by attenuated epithelium [3]. Sub-mucosal gland density is low in oedematous part of the polyp (fundus) and high in the neck (pedicle). Accompanying stroma is oedematous with a mononuclear cell and eosinophil infiltrate.

8.5.1 General Mucin Gene Expression Profile

Mucin expression was up-regulated in nasal polyps compared to normal inferior turbinate mucosa [10, 22, 37]. Intra-cellular mucin content in nasal polyps was 2.9 times higher than in healthy inferior turbinate mucosa [22]. All the nine mucin genes investigated so far (MUCs1–3, 4, 5AC, 5B and 6–8) have been found to be

expressed in nasal polyps [3, 22]. This is similar to mucin gene expression profiles reported for the lower and upper airway mucosa including normal and vasomotor inferior turbinates [5, 6]. Excluding MUC8 which was not included in our study, all the studied mucin genes were expressed in both epithelium and sub-mucosal glands of nasal polyps [3]. However, the expression pattern of individual mucin genes was widely variable among individual polyps and in different areas of mucin secretory elements within the same polyp. This wide variation of mucin gene expression among different polyps can be explained by the wide spectrum of local and systemic factors involved in polyp development and/or progression. Although the airway mucosa can express almost the whole set of mucin genes, in some extreme cases, the expression pattern can vary to the degree that some genes become completely down-regulated (blocked). Intra-polyp variation in mucin gene expression may be due to the differences of cell secretory stages and cell cycles at the time of tissue harvesting [5].

The predominantly expressed mucin genes in nasal polyps are MUC4, 5AC [3, 22] and MUC8 [22, 27] followed by MUC3, 1, 5B and 7. The least expressed mucin genes in the nasal polyps are MUCs2 and 6 [3]. Figure 8.1 illustrates averaged expression signals of the first eight mucin genes in nasal polyps from 20 patients based on the results in reference [3].

In situ hybridization demonstrated that there is significantly more glandular mucin gene expression in nasal polyps than in healthy sphenoid sinus mucosa. MUC1, 2 and 3 were expressed in sub-mucosal glands of nasal polyps, but not in sphenoid sinus mucosa. Average number of mucin genes expressed in the sub-mucosal glands of nasal polyps was 2.95 compared to 0.75 in sphenoid mucosa. Furthermore, averaged expression signals of mucin genes in the sub-mucosal glands were significantly more in nasal polyps than in sphenoid sinus mucosa [3]. This suggests that sub-mucosal glands play an important role in mucin gene expression in nasal polyps. Similar results have been reported in chronic sinusitis where quantitative analysis of mucin expression has demonstrated that the majority of mucin produced is of sub-mucosal gland origin [39]. This may indicate that, as a result of the inflammatory processes which resulted in the development of nasal polyps, sub-mucosal glands are exposed to more stress than the epithelium, with more mucin genes being expressed and existing genes up-regulated. Hyperplasia of sub-mucosal glands could be an additional process by which more mucin is produced. Peñia et al. [32] reported an increase in sub-mucosal gland area in sinus mucosa of children with chronic sinusitis as compared to controls.

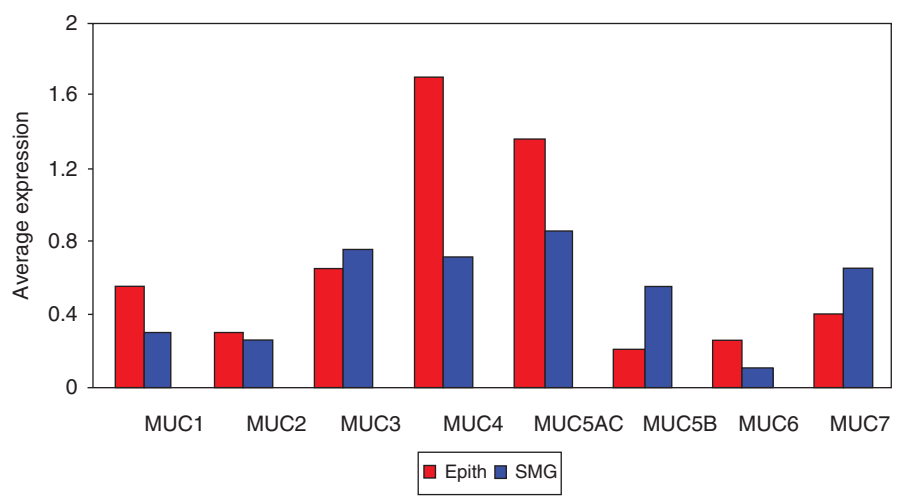

Fig. 8.1 Averaged expression signals of the first eight mucin genes in nasal polyps from 20 patients. Expression signals from 20 polyp patients were averaged for each mucin gene [in the epithelium and sub-mucosal glands separately] to show the average distribution and predominance of the different mucin genes in the epithelium and sub-mucosal glands. Weak expression signals were counted as 1, moderate signals as 2 and strong signals as 3. (Based on the results of Ali et al. [3])

8.5.2 Individual Mucin Genes

8.5.2.1 MUC1

MUC1 expression has been reported in normal inferior turbinate epithelium and nasal polyps with no significant difference in expression levels [22]. In our study, although in the majority of samples MUC1 expression was weak in both the polyp epithelium and sub-mucosal glands, epithelial MUC1 expression was more predominant in nasal polyps than in healthy sphenoid sinus mucosa. Glandular MUC1 expression was also detected in nasal polyps but not in control sphenoid sinus mucosa. Martínez-Antón et al. [27] have also reported MUC1 up-regulation in nasal polyps compared to healthy nasal mucosa. Interestingly, Aust et al. [6] noted MUC1 down-regulation in vasomotor inferior turbinates compared to normal turbinates. They speculated that decreased MUC1 expression might trigger the abnormal neurogenic signal leading to copious nasal secretion in vasomotor rhinitis.

8.5.2.2 MUC2

MUC2 encodes for a large secretory mucin which is mainly an intestinal mucin and provides a protective barrier between the intestinal epithelium and luminal contents. MUC2 up-regulation has been reported in maxillary sinus mucosa [43]. Kim et al. [22] found epithelial MUC2 up-regulation in three of six nasal polyp specimens compared to normal inferior turbinate epithelium. Their study did not include mucin gene expression in the sub-mucosal gland of nasal polyps or inferior turbinates. In our study, weak epithelial MUC2 expression was noted in nasal polyps and sphenoid sinus mucosa. However, no MUC2 expression was noted in the sub-mucosal glands of healthy sphenoid sinus mucosa while glandular MUC2 expression was detected in 20% of nasal polyps. Weak MUC2 mRNA expression in nasal polyps has also been reported by Martínez-Antón et al. [27].

8.5.2.3 MUC3 and 6

MUC3 encodes for a membrane-bound mucin which is mainly intestinal, while MUC6 gene encodes for a secretory mucin which is mainly gastric. Both mucins are thought to have an important protective rule in the gastro intestinal tract. Although MUCs3 and 6 expression was not found in normal or vasomotor inferior turbinate mucosa [6], it has have been reported in allergic nasal mucosa [36]. Depending on the previous results which showed no MUC3 or 6 expression in inferior turbinate mucosa [34], Kim et al. [22], excluded MUC3 and 6 from the set of mucin genes they studied in nasal polyps. Martínez-Antón et al. [27] excluded MUC3 in their study on mucin gene expression in nasal polyps and reported weak MUC6 expression in healthy nasal mucosa. In our study, MUC3 epithelial expression was detected in both nasal polyps and healthy sphenoid sinus mucosa while glandular MUC3 expression was detected in nasal polyps only. Weak MUC6 expression was detected in both the epithelium and sub-mucosal glands of nasal polyps, while no MUC6 expression was found in the epithelium or sub-mucosal glands of healthy sphenoid sinus mucosa.

8.5.2.4 MUC4

In our study, we found that MUC4 was the most predominantly expressed mucin gene in nasal polyps. It was expressed in the epithelium and sub-mucosal glands of 80 and 60% of nasal polyps respectively. This is similar to the results reported for normal and vasomotor nasal mucosa [6]. MUC4 up-regulation has also been reported in nasal polyps compared with healthy normal nasal mucosa [27] and inferior turbinate [7]. MUC4 was expressed in the epithelium of nasal polyps in the form of diffuse signals detected in all cell types along the epithelial layer and was not confined to the goblet cells. It was also expressed in squamous epithelium in areas of polyps with squamous metaplasia. Although MUC4 encodes for a membrane-bound mucin associated with the surface epithelium, MUC4 expression was also detected in the sub-mucosal glands of nasal polyps. However, sub-mucosal gland expression was weak in 35% of polyps and moderate in only 10% (compared to 65% of polyps showing moderate to strong epithelial expression). Average expression was ~2.5× as strong as in the epithelium [3].

MUC4 mucin (encoded by MUC4 gene) is unique in that its extra-cellular 3′ segment extends far higher than other membrane-bound mucins [17]. It also contains an

extra-cellular domain called AMOP (adhesion-associated domain in MUC4 and other proteins) which has not been identified in any other mucin genes [13]. MUC4 could have a role in signalling pathways involved in epithelial cell proliferation and differentiation [30] and in nasal polyps; MUC4 could be involved in epithelial hyperplasia and/or metaplasia.

8.5.2.5 MUC5AC

This mucin gene encodes for a major airway secretory mucin known to be mainly produced by goblet cells in airway epithelium [16, 20, 27]. Various studies have been reported on MUC5AC expression in nasal polyps with conflicting results. Kim et al. [20] have found MUC5AC mRNA expression in most of the goblet cells of nasal polyps; while in the healthy posterior ethmoid mucosa MUC5AC mRNA was barely expressed. Similar results have been reported by Lü et al. [26] and Burgel et al. [11] who found more MUC5AC expression in polyp epithelium compared to normal inferior turbinate mucosa. In our study, epithelial MUC5AC expression was detected in 75% of polyps compared to 25% in normal sphenoid sinus mucosa. However, Martínez-Antón et al. [27] reported MUC5AC mucin down-regulation in nasal polyps compared to normal nasal mucosa. Although MUC5AC is known as a goblet cell mucin, glandular MUC5AC has been reported in healthy and vasomotor inferior turbinate mucosa [6]. In our study, glandular MUC5AC expression was detected in 55% of nasal polyps and average expression was ~1.5× stronger in the epithelium than in the sub-mucosal glands [3].

8.5.2.6 MUC5B and 7

MUC5B gene encodes for a major airway mucin [44] while MUC7 is a major salivary mucin [9]. Both MUC5B and 7 are known to be expressed in the airways and their expressions are mainly in the sub-mucosal glands [6, 27, 38]. In our study, both MUC5B and 7 glandular expressions were identified in 40% of polyps compared to 20 and 25% respectively for epithelial expression of the two mucin genes. The average expression of MUC5B was >2.5 fold stronger in the sub-mucosal glands than in the epithelium [3]. Similar results of MUC5B up-regulation in nasal polyps compared to healthy nasal mucosa have been reported [27]. Similar to other mucin genes, MUC5B and 7 expressions are not restricted to the sub-mucosal glands as epithelial expression was identified in our study and has been reported in other studies [32, 46].

8.5.2.7 MUC8

MUC8 is expressed in the ciliated cells of human nasal epithelium [21]. In their study of mucin gene expression in nasal polyp and normal inferior turbinate epithelium, Kim et al. [22] reported MUC8 up-regulation in nasal polyp epithelium in five of six nasal polyp specimens compared to inferior turbinates. Similar results have been reported by Seong et al. [37]. In the study of Martínez-Antón et al. [27] MUC8 was highly expressed in both the epithelium and sub-mucosal glands of nasal polyps and normal nasal mucosa; however, marked variability of expression levels was noted and there was no significant difference between MUC8 expression in nasal polyps compared to normal nasal mucosa.

8.6 Steroids and Mucin Expression in Nasal Polyps

Although local and systemic steroid remain the mainstay medication for treatment of nasal polyps, the role of glucocorticoids in mucin gene expression in nasal polyps remains unclear. Various studies have investigated the effect of systemic and topical steroids on the expression of various mucin genes in nasal polyps with variable outcomes. Budisonide and beclomethasone dipropionate have been found to reduce mucus secretion in cultured nasal mucosa [35], and intravenous glucocorticoids resulted in reduced MUC8 expression in nasal polyps [45]. Furthermore, topical nasal fluticasone propionate and in vitro triamcinolone and dexamethasone have been found to inhibit MUC4 mRNA expression in nasal polyps and cultured nasal polyp epithelium, respectively [7]. However, other studies have shown that dexamethasone has no effect on steady-state mRNA levels of MUC2, MUC5AC or MUC8 in cultured human nasal epithelial cells [19] and that although intranasal fluticasone reduced eosinophils infiltration in nasal polyps, it had no effect on MUC5AC mucin expression [11].

8.7 Discussion

The aforementioned studies show that, as a part of the airway mucosa, nasal and sinus mucosa express a wide range of mucin genes comparable to that of the airway mucosa which is known to express the majority of the currently known mucin genes. The mucin genes studied in nasal polyps so far are the first nine mucin genes out of the currently known 20 mucin genes. More mucin genes are therefore expected to be expressed in nasal polyps. This is likely to complicate the whole profile of mucin expression in nasal polyps. The wide variability of mucin gene (and subsequently mucin protein) expression patterns reflects the extremely wide range of internal and external environmental factors involved in the development of nasal polyps which can alter the type and level of individual mucin gene expression. Therefore, it would be unrealistic to expect that a single treatment modality would be able to control all mucin genes expressed in nasal polyps or to be suitable for all cases of nasal polyps.

8.8 Future Work

Mucin gene and protein expression in sub-groups of nasal polyps, classified according to different clinical (physiological and pathological) variables, needs to be studied in detail in order to understand the role of these variables in the control of mucin gene expression in nasal polyps.

Detailed histochemical and cytochemical studies of distribution, density and functions of secretory elements in nasal polyps compared to their counter parts in healthy nasal and sinus mucosa are needed to advance our understanding of the role of these elements in both mucin gene and protein expression in nasal polyps and help targeting these elements with new treatment modalities to control their increased numbers and/or functions.

The role of different inflammatory mediators needs to be studied both in vitro and in vivo in order to obtain more insight of the control mechanisms of mucin gene expression at molecular levels. This is likely to help invent new treatment modalities to control the release and/or effect of these inflammatory mediators for more effective management of this common and challenging condition.

Take Home Pearls

- Nasal polyps express at least the nine mucin genes studied so far (MUCs1–4, 5AC, 5B and 6–8).
- MUCs1, 2, 4, 5AC, 5B and 8 are up-regulated in nasal polyps, the main role played by submucosal gland.
- The multiplicity of factors controlling mucin expression in nasal polyps explains this wide range.
- The effect of steroids on mucin gene expression in nasal polyps is unclear.
- Further studies are needed for better understanding and management of nasal polyps.

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