Original article

Corticosteroid therapy increases membrane-tethered while decreases secreted mucin expression in nasal polyps

Background: Mucus hypersecretion is a hallmark of nasal polyposis (NP). Corticosteroids (CS) are first-line treatment for NP, decreasing their size and inflammatory component. However, their effect on mucin production is not well-understood. The aim of this (pilot) study was to investigate CS effect on mucin expression in NP.

Methods: Patients were randomized in control (n = 9) and treatment (oral prednisone for 2 weeks and intranasal budesonide for 12 weeks; n = 23) groups. Nasal polyposis from nonasthmatic (NP; n = 13), aspirin-tolerant (NP-ATA; n = 11) and aspirin-intolerant (NP-AIA; n = 8) asthmatics were studied. Nasal polyposis biopsies were obtained before (w0) and after 2 (w2) and 12 (w12) weeks of CS treatment. Secreted (MUC5AC, MUC5B and MUC8) and membrane-tethered (MUC1, MUC4) mucins (immunohistochemistry) and goblet cells (Alcian blue-periodic acid Schiff) were quantified in both epithelium and glands. Rhinorrea and nasal obstruction were also assessed.

Results: At w2, steroids increased MUC1 (from 70 to 97.5) and MUC4 (from 80 to 100) in NP-ATA patients’ epithelium compared with baseline (w0). At w12, steroids decreased MUC5AC (from 40 to 5) and MUC5B (from 45 to 2.5) in NP-ATA patients’ epithelium and glands, respectively, compared with baseline. No mucin presented significant changes in NP-AIA patients. MUC5AC and MUC5B expression correlated with goblet and mucous cell numbers, respectively, and MUC5AC also with rhinorrea score.

Conclusions: These results suggest: (i) CS up-regulate membrane (MUC1, MUC4) while down-regulate secreted (MUC5AC, MUC5B) mucins; (ii) there exists a link between secreted mucin expression and goblet cell hyperplasia; and (iii) NP from AIA may develop resistance to CS treatment.
hypersecretion usually occurs in respiratory diseases, such as asthma, cystic fibrosis and chronic rhinosinusitis with or without nasal polyps (NP) (2).

Nasal polyposis is an upper airways inflammatory disease affecting 2–4% of general population, 10–15% of asthmatic patients and over 90% of patients with aspirin-intolerant asthma (AIA) (12). Mucus hypersecretion, in the form of rhinorrea, is a common symptom of patients suffering from inflammatory sinonasal diseases, including NP. However, the mucin composition and its physiological role in the mucus overproduction of NP have not been deeply investigated. Although identical mucins and with a similar distribution have been found in healthy nasal mucosa and NP (9, 13, 14), these tissues differ in mucin amount. For instance, MUC1, MUC4, MUC5B and MUC8 mucins have been found increased while MUC2 and MUC5AC decreased in NP compared with healthy nasal mucosa (13). These differences could be partly due to goblet cell hyperplasia (GCH) usually present in airway diseases. In fact, changes in mucin production associated to GCH have been described in NP (15, 16).

Corticosteroids (CS) are the first line of therapy for the treatment of NP inducing a decrease in polyp size and inflammatory component (12, 17). Corticosteroids are known to decrease inflammation also in diseases such as asthma, cystic fibrosis and bronchitis (12, 18, 19), but their effects on mucus hypersecretion has been controversial. Although some works have studied CS effect on mucin expression in respiratory primary and culture cell lines, few studies have dealt with this topic in an in vivo situation and in a real disease.

In order to ascertain whether CS treatment represents a beneficial therapy for the mucus hypersecretion observed in NP, in the present (pilot) study we have investigated the in vivo effect of CS in both secreted (MUC5AC, MUC5B and MUC8) and membrane-tethered (MUC1, MUC4) mucins from NP. In addition, we have also assessed the effect of CS on the two main symptoms of NP (12), rhinorrea and nasal obstruction, and their correlation with mucin expression.

## Methods

### Study population

A total of 32 consecutive patients with severe NP, including patients without asthma, and with either aspirin-tolerant (ATA) or AIA, were included in this prospective and randomized study. All patients signed informed consent and the study was approved by the Ethics Committee of our Institution. In our study population, 20% of patients were atopic while 30% were female, this percentage increasing in the AIA group (50%), in agreement with previous studies (20) (Table 1).

### Inclusion and exclusion criteria

All patients included in this study showed severe NP based on polyp size by nasal endoscopy (Lildholdt mean score: 2.7 over 3) (21) and bilateral sinus opacification by computed tomography (CT) scan.

### Immunohistochecistry

The indirect immunoperoxidase technique was performed on 3-μm sections of paraffin-embedded tissue sections for the detection of membrane-tethered (MUC1 and MUC4) and secreted (MUC5AC, MUC5B, MUC8) mucins, as previously described (13). The monoclonal antibody M8 recognizing MUC1 was used as undiluted hybridoma supernatant (23). Polyclonal anti-MUC4 (24) and anti-MUC8 (25) antibodies, and rabbit polyclonal serum LLUM5.1 (26) and LUM5B.2 (27) recognizing non-TR regions of MUC5AC and MUC5B, respectively, were also used. B12 MoAb (Dr Castro, Barcelona, Spain) recognizing a synthetic dextran molecule and preimmune rabbit serum were used as negative controls.

### Quantification analysis

Sections were examined by light microscopy (×400) and the patterns of antibody staining were scored in a quantitative manner. The pattern of reaction was analysed in both, the epithelium and SMGs, the number of immunoreactive positive cells (brown staining) being expressed as a percentage of total cell number (500 counted cells).

### Glucocorticoid effect on mucin expression in nasal polyps

#### Table 1. Epidemiological characteristics of study patients

<table>
<thead>
<tr>
<th>Nasal polypos (NP) type</th>
<th>n</th>
<th>Age (years)*</th>
<th>Female, n (%)</th>
<th>Atopy, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>32</td>
<td>54.2 ± 2.8</td>
<td>10 (31)</td>
<td>6 (19)</td>
</tr>
<tr>
<td>Control group</td>
<td>9</td>
<td>54.4 ± 5.5</td>
<td>2 (22)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>No asthma</td>
<td>3</td>
<td>44.3 ± 6.4</td>
<td>0</td>
<td>1 (33)</td>
</tr>
<tr>
<td>Asthma</td>
<td>6</td>
<td>59.5 ± 7.0</td>
<td>2 (33)</td>
<td>0</td>
</tr>
<tr>
<td>Aspirin-tolerant</td>
<td>4</td>
<td>63.5 ± 8.7</td>
<td>1 (25)</td>
<td>0</td>
</tr>
<tr>
<td>Aspirin-intolerant</td>
<td>2</td>
<td>51.5 ± 13.5</td>
<td>1 (50)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment group</td>
<td>23</td>
<td>54.1 ± 3.4</td>
<td>8 (35)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>No asthma</td>
<td>10</td>
<td>56.0 ± 5.0</td>
<td>3 (30)</td>
<td>3 (30)</td>
</tr>
<tr>
<td>Asthma</td>
<td>13</td>
<td>52.6 ± 4.7</td>
<td>5 (38)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Aspirin-tolerant</td>
<td>7</td>
<td>51.3 ± 8.0</td>
<td>2 (29)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>Aspirin-intolerant</td>
<td>6</td>
<td>54.1 ± 5.1</td>
<td>3 (50)</td>
<td>1 (17)</td>
</tr>
</tbody>
</table>

*Mean ± standard error of the mean (SEM).

The diagnosis of aspirin intolerance was made on the basis of a clear-cut history of asthma attacks precipitated by nonsteroidal anti-inflammatory drugs. In asthmatic patients with doubtful diagnostic, aspirin sensitivity was tested by nasal challenge with lysine acetylsalicylic acid and acoustic rhinometry outcomes (22). Asthmatic patients, depending on their severity, received inhaled steroids and/or beta-2 agonists but not leukotriene antagonists. This treatment of asthma was not modified during the study. None of the patients had cystic fibrosis and those with steroid contraindications were excluded from the study.

### Study design

The study design used herein was as follows: after a washout period of 4 weeks for intranasal and 3 months for oral CS, patients were randomized (3 : 1) in: group A, the CS-treated group (n = 23) received oral prednisone (30 mg daily for 4 days followed by a 2-day tapered reduction of 5 mg) and intranasal budesonide (400 μg/twice a day) for 2 weeks (w2), followed by intranasal budesonide alone for 10 additional weeks (w12); and group B, the nontreated control group (n = 9) did not receive any steroid treatment over a 2-week period (w2). For ethical reasons, patients from the control group were not kept with ineffectual treatment for more than 2 weeks. Nasal polyp biopsies were obtained at w0, w2 and w12 in both A and B groups.
The immunoreactivity score was assessed by two independent observers in a blind manner, and the results averaged. The level of mucin expression was classified in high (>70% to 100%), moderate (>30% to 70%) and poor (0% to 30%) depending on their percentage of cell positivity.

Goblet cell staining

In order to assess changes in the number of goblet cells before and after CS treatment, Alcian blue-periodic acid Schiff (AB-PAS) staining was performed. Positive cells with purple/blue color were counted by light microscopy (×400) and expressed as a percentage of total epithelial cells (500 cells counted).

Nasal symptoms

Rhinorrea and nasal obstruction were assessed at w0, w2 and w12. The severity of nasal symptoms was scored as follows: 0, no symptom; 1, mild but not troublesome; 2, moderate symptom somewhat troublesome; and 3, severe and troublesome that interferes with the daily activity or sleep.

Statistical analysis

Mucin data was expressed as median and 25–75th percentile of positive cells among total cells. The nonparametric statistical Mann–Whitney U-test was used for between-group comparisons and the Wilcoxon test was used for paired comparisons of the expression of mucins before and after CS treatment. Rho Spearman’s analysis was used to assess the correlation between mucin gene expression and goblet cell number in the different tissues, as well as to correlate mucin expression and nasal symptoms. Statistical significance was set at P < 0.05.

Results

Expression of MUC genes at baseline

At w0, there were no significant differences in mucin expression between CS-treated and control groups neither at epithelial nor at glandular level (Table 2).

Membrane-tethered mucins. At w0, MUC1 was highly detected in NP epithelium and glands whereas MUC4 was highly detected in the epithelium but poorly detected in SMG (Table 2). Regarding the epithelial mucin expression in the different groups of NP, a nonsignificant increase was found in the AIA group compared with nonasthmatic and ATA patients (Fig. 1A,B). Membrane-tethered mucins showed no variations between groups in glands.

Secreted mucins. Mucin expression levels were high for MUC8, moderate for MUC5AC and poor for MUC5B in the epithelium. In glands, MUC5B and MUC8 were moderately detected while MUC5AC was poorly expressed (Table 2). In the epithelium, MUC5AC in ATA (median, 25–75th percentile: 40, 35–60) and MUC8 in AIA (100, 100–100) groups showed an increased expression compared with nonasthmatic patients (MUC5AC: 20, 10–30; MUC8: 75, 55–92.5; P < 0.05) (Figs 1C and 2A,C). In glands, MUC5B was found decreased in AIA patients (5, 1.3–23.4) compared with ATA (45, 12.5–56.3; P < 0.05) and nonasthmatic (35, ns) patients (Fig. 1D).

Mucin regulation by 2 weeks of both oral and intranasal corticosteroids

No significant differences in mucin expression were found in controls between w0 and w2 in the epithelium. Nonsignificant increases were observed in glands (Table 2).

Membrane-tethered mucins. At w2, membrane-tethered mucins increased in the epithelium of the treated group compared with w0 while no variations were found in glands (Table 2).

Regarding the different subgroups, MUC1 increased at w2 compared with w0 in both nonasthmatic (w0: 80, w2: 87.5; ns) and ATA (w0: 70, w2: 97.5; P < 0.05) patients,

Table 2. Mucin protein expression in nasal polyps (NP) detected by immunohistochemistry

<table>
<thead>
<tr>
<th>Mucin</th>
<th>C-w0</th>
<th>C-w2</th>
<th>T-w0</th>
<th>T-w2</th>
<th>T-w12</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUC1</td>
<td>Epithelium</td>
<td>80 (70–88)</td>
<td>85 (71–94)</td>
<td>80 (70–90)</td>
<td>90 (80–100)**</td>
</tr>
<tr>
<td></td>
<td>Glands</td>
<td>35 (8–63)</td>
<td>73 (54–88)</td>
<td>73 (34–80)</td>
<td>73 (28–90)</td>
</tr>
<tr>
<td>MUC4</td>
<td>Epithelium</td>
<td>95 (90–100)</td>
<td>100 (100–100)</td>
<td>90 (70–100)</td>
<td>100 (90–100)</td>
</tr>
<tr>
<td></td>
<td>Glands</td>
<td>5 (0–23)</td>
<td>10 (3–18)</td>
<td>0 (0–3)</td>
<td>5 (0–8)</td>
</tr>
<tr>
<td>MUC5AC</td>
<td>Epithelium</td>
<td>25 (9–38)</td>
<td>23 (11–80)</td>
<td>30 (14–51)</td>
<td>28 (8–53)</td>
</tr>
<tr>
<td></td>
<td>Glands</td>
<td>0 (0–3)</td>
<td>8 (3–18)</td>
<td>0 (0–3)</td>
<td>3 (0–3)</td>
</tr>
<tr>
<td>MUC5B</td>
<td>Epithelium</td>
<td>1 (0–3)</td>
<td>3 (0–3)</td>
<td>0 (0–3)</td>
<td>3 (0–3)</td>
</tr>
<tr>
<td></td>
<td>Glands</td>
<td>10 (5–80)</td>
<td>60 (13–85)</td>
<td>30 (5–45)</td>
<td>30 (8–45)</td>
</tr>
<tr>
<td>MUC8</td>
<td>Epithelium</td>
<td>98 (73–100)</td>
<td>100 (100–100)</td>
<td>90 (88–100)</td>
<td>100 (93–100)</td>
</tr>
<tr>
<td></td>
<td>Glands</td>
<td>8 (1–10)</td>
<td>28 (2–70)</td>
<td>8 (2–58)</td>
<td>10 (3–40)</td>
</tr>
</tbody>
</table>

Results are expressed as median and 25–75th percentile. C-w0, control group at baseline (week 0); C-w2, control group after 2 weeks without treatment; T-w0, treated group at baseline (week 0); T-w2, treated group after 2 weeks of oral and intranasal corticosteroids (CS); T-w12, treated group after 12 weeks of intranasal CSs.

Wilcoxon test: *P < 0.05, and **P < 0.01 compared with T-w0; ***P < 0.05, and ****P < 0.01 compared with T-w2.
and MUC4 in ATA patients (w0: 80, w2: 100; P = 0.06) (Fig. 1A,B). Interestingly, polyps from AIA patients showed no variations after 2 weeks of steroid treatment. In glands, no variations were found in any of the studied groups.

**Secreted mucins.** At w2, secreted mucins showed no significant variations compared with w0, neither in the epithelium nor in glands (Table 2).

**Mucin regulation by 12 weeks of intranasal corticosteroids**

**Membrane-tethered mucins.** In the epithelium, both membrane-tethered mucins (MUC1, MUC4) showed a similar pattern of regulation by CSs, increasing at w2 and returning to basal levels at w12 while no variations were detected in glands (Table 2). In the epithelium, MUC1 expression decreased in w12 respect to w2 in both nonasthmatics and ATA patients but not in AIA reaching w0 levels, suggesting that the increase detected after oral steroids therapy was not maintained by long-term intranasal steroids in none of these groups (Fig. 1A). At w12, MUC4 showed a trend to decrease in ATA patients and to return to basal levels (w0) (Fig. 1B).

**Secreted mucins.** After 12 weeks of intranasal steroid treatment, secreted mucins, MUC5AC and MUC5B, showed a significant decrease compared with w0 and w2 in the epithelium and glands, respectively (Table 2).

Regarding the different subgroups, MUC5AC showed a significant decrease in the epithelium at w12 compared with w0 and w2 in the asthmatic group, mainly in ATA patients (w0: 40, 35–60; w2: 15, 10–60; w12: 5, 1.3–10; P < 0.05) (Figs 1C and 3A,C). A similar but not significant decrease pattern was found for MUC5B in glands in both nonasthmatic (w0: 35, w2: 20, w12: 12.5; ns) (Fig. 1D) and ATA (w0: 45, w2: 30, w12: 2.5; P = 0.06) (Figs 1D and 4A,C) patients. This decrease was not observed in the AIA group (Fig. 1D). In the epithelium, the soluble mucin MUC8 was found markedly increased in nonasthmatics at w12 (100; P = 0.06) compared with w0 (75) and slightly increased compared with w2. Moreover, although the expression of MUC8 in NP glands showed a high variability, especially in asthmatic patients, a significant increase in MUC8 was found in ATA patients at w12 (45; 8.7–85, P < 0.05) compared with w0 (2.5; 0–6.2) (Fig. 2B,D) and w2 (2.5; 1.3–75).

**Mucins and goblet cells**

Alcian blue-periodic acid Schiff staining was observed in epithelial goblet cells and mucous cells of SMG from NP biopsies. While goblet cells stained exclusively blue, mucous cells in glands stained mainly blue, but also pink or purple, when acidic and neutral mucins were jointly expressed. A decrease in goblet cell number was observed after both oral (w2) and intranasal (w12) CS treatment, specifically in ATA patients (Fig. 3B,D). The decrease on
goblet cell content in the epithelium correlated with MUC5AC \( (r: 0.725; P < 0.01) \) (Fig. 3). In addition, a correlation with the AB-PAS staining pattern in glands mucous cells was also found for MUC5B \( (r: 0.782, P < 0.01) \) (Fig. 4).

Figure 2. Photomicrographs of MUC8 expression in the epithelium of NP from nonasthmatic (A) and AIA (C) patients at baseline (w0) and in the glands of NP-ATA before (B) and after (D) 12 weeks of CS treatment. ep, Epithelium; gl, glands (original magnification: ×400).

Figure 3. Photomicrographs of MUC5AC (A and C) and Alcian blue-periodic acid Schiff (AB-PAS) staining for goblet cell detection (B and D) in the epithelium (ep) of NP-ATA patients. Changes in MUC5AC mucin due to corticosteroid (CS) therapy correlate with changes in goblet cell (arrows) amount in the epithelium (original magnification: ×400).

Nasal symptoms

Control group showed no variations over the time on nasal symptoms. At w0, there were no significant differences in rhinorrea and nasal obstruction scores...
between treated and control groups. At w2, treated patients showed a significant improvement in nasal obstruction (w0: 3, 2–3; w2: 0, 0–1) and rhinorrea (w0: 3, 2–3; w2: 0, 0–2) compared with w0. At w12, intranasal budesonide maintained the improvement in both nasal obstruction (0, 0–2) and rhinorrea (1, 0–2), similar to w2 (Table 3). No significant differences at baseline (w0) were found between asthmatic and nonasthmatic or ATA and AIA patients. At w2, the improvement on nasal obstruction was higher in asthmatics (3, 1.5–3; \( P < 0.01 \)) than in nonasthmatic (1, 0–1.3) patients.

A significant correlation was observed between the improvement in rhinorrea and the reduction of MUC5AC after treatment \((r = 0.403, \ P < 0.05)\). MUC5B showed a similar tendency but with no significance. No correlation was found between secreted mucin expression and nasal obstruction.

### Discussion

In the present study, different regulation patterns by CSs were observed depending on the type of mucins, secreted vs membrane-tethered, on the duration of steroid treatment, short courses vs long-term therapy and on the phenotypic characteristics of NP. While a short-term treatment with oral prednisone combined with intranasal budesonide seemed to up-regulate membrane-tethered mucins (MUC1 and MUC4) in almost all NP epithelia and the long-term therapy failed to maintain this effect, secreted mucins MUC5AC and MUC5B appeared to strongly respond to the long-term treatment by decreasing their expression in the epithelium and glands, respectively. This is at variance with two previous studies in which no variations were found in MUC5AC expression after either 8 weeks of intranasal fluticasone in NP (28) or 1 month of intranasal budesonide in lung polyps.

![Figure 4. Photomicrographs of MUC5B (A and C) and Alcian blue-periodic acid Schiff (AB-PAS) staining for mucous cell detection (B and D) in submucosal glands (SMGs) (gl) of NP-ATA patients. Changes in MUC5B mucin due to corticosteroid (CS) therapy correlate with changes in the number of mucous cells of SMGs glands (original magnification: \( \times 200 \)).](image)

Table 3. Effect of oral and intranasal corticosteroids (CS) on nasal symptoms in nasal polyp (NP) patients

<table>
<thead>
<tr>
<th>Nasal symptoms</th>
<th>Control group (C)</th>
<th>Treatment group (T)</th>
<th>Improvement after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C-w0</td>
<td>C-w2</td>
<td>T-w0</td>
</tr>
<tr>
<td>Rhinorrea</td>
<td>3.0 (2.0–3.0)</td>
<td>2.5 (1.0–3.0)</td>
<td>3.0 (2.0–3.0)</td>
</tr>
<tr>
<td>Obstruction</td>
<td>3.0 (2.8–3.0)</td>
<td>3.0 (2.0–3.0)</td>
<td>3.0 (2.0–3.0)</td>
</tr>
</tbody>
</table>

Results are expressed as median and 25–75th percentile. C-w0, control group at baseline (week 0); C-w2, control group after 2 weeks without treatment; T-w0, treated group at baseline (week 0); T-w2, treated group after 2 weeks of oral and intranasal CSs; T-w12, treated group after 12 weeks of intranasal CSs. Wilcoxon test: *\( P < 0.01 \) compared with T-w0; **\( P < 0.01 \) compared with C-w2.
tissue biopsies (29). These differences could be explained by the small number of patients analysed in both studies as well as to the short duration of treatment. In agreement with our findings, several in vitro studies have reported that dexamethasone decreases MUC5AC mRNA in airway epithelial cell lines (30–32), primary normal human bronchial epithelial (NHBE) cells (32) and rat primary airway epithelial cells (31) while dexamethasone increased MUC1 in cancer cell lines (33, 34).

These different regulation patterns might reflect a variety of pathophysiological roles of mucins in mucus production and secretion. Given that MUC5AC and MUC5B are the major mucins found in respiratory tract secretions (26, 35) they might play an important role in mucus formation. Therefore, the down-regulation caused by CSs in MUC5AC and MUC5B levels could result in a decrease of mucus hypersecretion from NP. In this direction, down-regulation of MUC5AC after CS treatment clearly correlated with the improvement of rhinorrhea in all groups of NP patients. Completely different functions have been described for the two membrane-tethered mucins here studied. MUC1 has been reported to be involved in metastasis, angiogenesis and immune regulation (33, 36, 37) while MUC4 has been identified as a ligand of ErbB2 (38), a receptor that modulates epithelial cell proliferation following damage in airways of asthmatics (39). The increase of MUC1 and MUC4 levels after CS treatment may be related to the epithelial repairing and remodeling processes in which they seem to be involved.

Although MUC8 has been reported to be increased in chronic rhinosinusitis and NP compared with healthy nasal mucosa (13, 40), its potential role as one of the major compounds of mucus has not been well-established. In the present study, CS treatment increased MUC8, like membrane-tethered mucins, with a maximum response after long-term CSs. Since MUC8 does not seem to be a major secreted mucin, the different CS regulation pattern of MUC8 compared with other secreted mucins could account for a different role of this mucin in NP.

Since NP is an inflammatory disease affecting 10–15% of asthmatic patients and over 90% of patients with AIA, a special attention was paid to these groups of patients.

The groups of NP patients showed a differential response to CS therapy. Nasal polyps from ATA showed the most significant changes for all analysed mucins, while those from nonasthmatics showed variations in MUC1, MUC5B and MUC8, and those from AIA patients showed changes almost exclusively in MUC5AC, suggesting a trend of resistance to CS treatment. In accordance to these findings, aspirin sensitivity has been reported to be a risk factor for steroid resistance in patients with NP (41) as well as in steroid nonresponder severe asthmatic (42). A greater inflammatory component and/or a reduced number of CS receptors in AIA patients could account for its CS resistance. Another potential explanation for this lack of response could be the high basal levels of membrane-tethered mucins and the low levels of secreted mucins in AIA patients, almost comparable with the levels found in ATA patients after CS treatment.

Goblet cell hyperplasia has been reported in airways diseases such as NP (15) and asthma (43, 44). In a GCH rat model, CSs inhibited the hyperplasia induced by tobacco smoke (45) and neutrophils products (46). In this sense, since CSs could decrease GCH, the changes in mucin content found in our NP biopsies after CS treatment might be due to changes in the number of goblet cells. In fact, a correlation was found between MUC5AC expression and goblet cell numbers, as well as between mucous cells in SMG and MUC5B. Since MUC1, MUC4 and MUC8 are not goblet cell-specific mucins we could speculate that their increase after CS treatment might be explained by an increased number of nongoblet cells (basal, ciliated) that might take place in NP epithelium to counteract the decrease of goblet cell number after CS treatment. Although there are no studies dealing with CS effects on GCH in NP, Laitinen et al. have demonstrated that long-term treatment of asthmatic subjects with inhaled CS significantly increased the ratio of ciliated cells to goblet cells in the airways (47). However, other steroid effects should be taken into account: CSs could exert their action directly regulating MUC gene expression (32) or indirectly through their inhibitory effects on pro-inflammatory cytokines (48).

In conclusion, our study demonstrates that a short course of oral steroids increases membrane-tethered (MUC1 and MUC4) mucins and that long-term intra-nasal steroid treatment is able to decrease major secreted mucins (MUC5AC and MUC5B). The down-regulation of secreted mucins could result from the ability of CSs to reduce GCH, and could account for the reduction of mucus production and rhinorrhea. Since CSs are capable to reduce the number of the main mucin-producing cells and they also decrease rhinorrhea, our results suggest that CS may be considered a beneficial therapy for mucus hypersecretion in NP. Notwithstanding that, regarding mucin expression, patients with NP and aspirin-sensitive asthma seems to show a trend of resistance to CS treatment.

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