Corticosteroid Use Does Not Alter Nasal Mucus Glucose in Chronic Rhinosinusitis

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objectives. To evaluate nasal mucus glucose concentrations in patients with and without chronic rhinosinusitis and determine if corticosteroid therapy alters mucus glucose.

Study Design. Prospective observational study.

Setting. Single tertiary care center.

Subjects. Ninety-five patients presenting to an otolaryngology clinic.

Methods. Participants completed questionnaires that included a history of medical and surgical therapies as well as sinusitis-specific quality-of-life measurements. Nasal mucus was collected in an outpatient clinic using an open cell foam technique. The nasal mucus glucose concentrations of patients with and without chronic rhinosinusitis were compared to the use of systemic and topical glucocorticoid treatment.

Results. A statistically significant difference was measured between mean nasal glucose secretions of control patients, 10.2 mg/dL, compared with patients diagnosed with chronic rhinosinusitis, 18.4 mg/dL (P < .0001). Use of corticosteroids, both topical and systemic, did not correlate with nasal glucose concentrations.

Conclusion. Patients diagnosed with chronic rhinosinusitis have elevated nasal glucose concentrations compared with control patients, and this elevated nasal glucose level was independent of corticosteroid use. Nasal glucose may independently contribute to the pathophysiology of chronic rhinosinusitis.

Keywords

chronic rhinosinusitis, solitary chemosensory cell, innate immunity, glucocorticoid

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The sinonasal cavity serves as the first line of defense of the respiratory tract. While inhaling fungal spores, bacteria, and viral particles, the innate immune mechanisms continuously work to maintain an environment free of infection. Upper airway innate immunity is dependent on mucociliary clearance as well as the production of antimicrobial compounds including nitric oxide, lactoferrin, cathelicidins, and defensins.1-4 Impaired innate defense mechanisms can lead to mucostasis, biofilm formation, and recurrent or chronic infections, a hallmark of chronic rhinosinusitis (CRS).5

Emerging evidence is mounting supporting the role of sweet and bitter G-protein–coupled taste receptors as a novel arm of sinonasal innate immunity. The bitter taste receptors, known as type 2 taste receptors (T2Rs),6 were initially described in the tongue to recognize toxic or spoiled foods.7 Recently, T2Rs have been identified in the ciliated cells of the respiratory epithelium8 and found to detect microbial quorum-sensing molecules, subsequently triggering local innate antimicrobial defenses through the production of nitric oxide, yielding direct bactericidal activity as well as increasing mucociliary clearance.9

In addition to bitter taste receptors expressed in ciliated cells, taste receptors have also been identified in discrete, nonciliated solitary chemosensory cells (SCCs) that populate the respiratory epithelium.10-12 T2Rs on SCCs regulate a complementary innate defense through the release of antimicrobial peptides (AMPs) from the surrounding epithelial cells.11 In addition to expressing T2Rs, SCCs also express the sweet taste receptor, T1R2/3.12 Stimulation of the T1R2/3 by glucose inhibits the propagation of the T2R signaling, and thus, we have proposed that the sweet taste receptor may act as a “rheostat” to control the magnitude of the T2R response depending on the glucose concentration in the airway surface liquid (ASL). Depletion of ASL glucose concentration via bacterial glucose consumption (an indirect
measure of local bacterial density/population) may signal the onset of an infection and play a role in the activation of T2R-mediated AMP secretion. The T1R2/3 sweet receptors in SCCs function to block the T2Rs response to bitter compounds secreted by some bacteria during low-level colonization. However, this blockade is relieved when bacterial numbers increase enough to cause depletion of ASL glucose.11,14,16

Respiratory mucus glucose concentration is tightly regulated and results from a balance of tonic glucose leakage through the airway epithelium as well as uptake into the airway cells via apical transporters.17-19 Upsetting this balance can alter mucus glucose concentration, as observed in diabetic patients with elevated blood glucose levels (hyperglycemia) who have a resulting increased flux of glucose into their mucus.19,20 Our prior work has demonstrated that CRS patients have elevated ASL glucose independent of blood glucose levels,11 most likely from increased leak caused by breakdown of the epithelial barrier as a consequence of chronic infection and inflammation.17 Both in patients with diabetes and in patients with CRS, the increased glucose in nasal mucus has the potential to disrupt the defensive function of SCCs discussed above.

Both topical and systemic application of corticosteroids are commonly used therapies for adult rhinosinusitis.21,22 Systemic corticosteroids are known to induce systemic hyperglycemia during the treatment of many inflammatory conditions.23 Thus, the current study aimed to (1) confirm the presence of elevated glucose concentrations in the nasal mucus of CRS patients and (2) determine whether systemic or topical corticosteroid use correlates with elevated nasal mucus glucose levels.

Methods

After receiving institutional review board approval from the hospital of the University of Pennsylvania, patients who presented to the rhinology clinic were enrolled for nasal mucus sampling. Nasal mucus of 95 subjects who met the requirement for enrollment was sampled from July 2013 through December 2013. Patients were enrolled consecutively during an outpatient office visit unless an individual refused to participate or met any of following exclusion criteria: age younger than 18 years, history of sinonasal surgery within 8 weeks of presentation, antibiotic use within 6 weeks, or prior head and neck radiation treatment.

A thorough patient history was obtained that included a history of sinonasal infections, allergic rhinitis, use of antibiotics, as well as current use of topical or systemic steroids. CRS diagnosis in this study was characterized based on a prior history of 12 weeks of sinonasal symptoms as well as examination findings consistent with rhinosinusitis. Physical examination findings included mucosal edema or erythema, nasal polyposis, or nasal drainage identified on photomicroscopy.24 Disease-specific quality of life was measured using the Sinonasal Outcome Test–22 (SNOT-22) at the time of sampling.25

Nasal secretions were collected from patients using Pope ear wicks. The sponges were prepared by hydrating the sponge with sterile water and then dried in a tissue culture hood overnight under sterile conditions. Prepared dried sponges were inserted between the nasal septum and inferior turbinate bilaterally without topical anesthetic. They were left in place for 5 minutes and then retrieved and stored in a 1.5-mL Eppendorf conical tube (Eppendorf, Hamburg, Germany). A 22-g needle was used to pierce a small hole in the bottom of the Eppendorf tube containing the sponge, which was then placed inside a second Eppendorf tube and centrifuged at 600g for 5 minutes. The secretions were collected in the bottom Eppendorf tube and frozen in a −20°C freezer for a maximum of 2 weeks.

Collected nasal mucus glucose concentrations were measured in duplicate using a glucose colormetric assay (Cayman Chemical Company, Ann Arbor, Michigan).

Statistical analysis was performed using Prism 6 statistical software (GraphPad, La Jolla, California). In addition to standard statistical calculations, an unpaired 1-sided t test was used in comparison of the groups. The statistical significance level was established at P < .05.

Results

We evaluated nasal mucus glucose concentration in 95 patients, 15 patients with no history or symptoms of rhinitis and 80 patients who met the objective and subjective criteria for CRS.24 As demonstrated in Figure 1, there was a significantly elevated level of nasal mucus glucose concentration in patients with CRS, 18.4 ± 1.6 mg/dL, compared with controls, 10.1 ± 1.2 mg/dL (P < .0001). There were nearly identical nasal glucose levels measured among CRS patients with nasal polyposis, 18.3 ± 2.0 mg/dL, compared with CRS without polyposis, 18.5 ± 2.4 mg/dL.

We next determined whether topical corticosteroid treatment correlated with altered nasal mucus glucose concentration. The exact time of the last administration of topical steroids was not recorded, but all patients within this subset had used topical steroids within the preceding 24 hours. Figure 2 demonstrates that the nasal mucus glucose concentration was similar among CRS patients using and not
using topical steroids. This subset of patients using topical steroids was further stratified into those individuals using nasal irrigation to administer topical corticosteroids (17.7 ± 2.1 mg/dL) compared with those using aerosolized nasal spray (23.8 ± 3.9 mg/dL), which was not statistically significant (P = .17).

We also investigated whether systemic corticosteroid therapy correlated with altered nasal mucus glucose. As demonstrated in Figure 3, no significant difference in glucose concentration was identified among CRS patients taking oral corticosteroids, 19.1 ± 4.2 mg/dl, compared with those subjects taking no glucocorticoids, 17.0 ± 1.4 mg/dL.

Lastly, the CRS patient population contained more comorbid conditions including asthma and diabetes mellitus (DM) compared with the control subjects, as noted in Table 1. The patient history of DM did not appear to significantly alter the nasal mucus glucose concentration among CRS subjects. Nine individuals with CRS and DM had a mean nasal mucus glucose concentration of 19.5 mg/dL, which was comparable with 18.3 mg/dL among nondiabetic subjects with CRS. In addition, CRS subjects also had a higher prevalence of individuals diagnosed with asthma, 56.7%, compared with controls, 6.7%. This finding of concurrent asthma and rhinosinusitis is consistent with the unified airway hypothesis and overlapping clinical and pathologic features of the diseases. 26

Table 1. Clinical Characteristics of Subjects Enrolled for Nasal Mucus Sampling.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Controls</th>
<th>Chronic Rhinosinusitis Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects</td>
<td>15</td>
<td>80</td>
</tr>
<tr>
<td>Nasal polyposis</td>
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<td>48</td>
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<tr>
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<td>46</td>
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<td>Allergic fungal sinusitis</td>
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<td>9</td>
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<tr>
<td>Oral steroids</td>
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<td>13</td>
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<td>Topical steroids</td>
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<td>64</td>
</tr>
</tbody>
</table>

Discussion

G-protein–coupled taste receptors are emerging as a new arm in the respiratory epithelial innate immunity. Bitter agonists activate T2R-mediated cellular responses that can drive complementary innate defense mechanisms in the respiratory epithelium including an increase in cilia beat frequency, nitric oxide production, and release of AMPs. 8,9,11,16 It has been demonstrated that airway T2Rs detect molecules secreted by microbes, such as quorum-sensing molecules, 9,27 and activate the local defenses discussed above.
Our prior in vitro work demonstrated a dose-dependent inhibition of the SCC T2R-mediated release of AMPs with topical application of glucose. This in vitro observation motivated our interest in sampling nasal mucus glucose concentrations among CRS subjects and controls. The current study identified patients with CRS to have a statistically significant elevation in nasal glucose concentration compared with control patients, and the elevated nasal mucus glucose level is in a range that inhibits the SCC T2R-mediated antimicrobial activity. Our current findings confirm our prior observation that CRS patients have elevated nasal mucus glucose levels compared with control patients. However, our values are not in exact agreement with our previously published values, which were higher in the CRS patients. In the current study, all samples were obtained in patients in the outpatient clinic setting, while in our prior study, some samples were collected in the operating room after intubation. Whether positive pressure ventilation or other components of anesthesia induction stimulate higher nasal mucus glucose will need to be further studied.

Our working model proposes that bacterial proliferation, in a healthy sinonasal cavity, leads to the consumption and depletion of nasal mucus glucose, thereby relieving the glucose inhibition of the T2R release of AMPs. However, patients suffering from CRS have elevated nasal mucus glucose levels and thus tonically inhibit the SCC T2R pathway that may contribute to unchecked bacterial proliferation.

In this study, we demonstrate that topical or systemic steroid use does not significantly alter nasal mucus glucose concentrations. Elevated glucose levels in CRS patients appear independent of pharmacologic effects and potentially explain an inherent acquired innate immune deficiency. While the exact mechanism that induces the elevated glucose levels in the respiratory epithelium is unknown, the antimicrobial benefit of low glucose concentrations has been previously established. Lower airway epithelial cells grown at an air-liquid interface have identified low levels of mucus glucose concentrations to be critical in maintaining airway sterility after exposure to bacteria. Low nasal glucose concentrations in cystic fibrosis patients were also found to be associated with decreased growth of *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Conversely, higher airway mucus glucose concentrations in diabetic patients may contribute to previous observations that diabetic patients are more prone to some airway infections than nondiabetic patients.

**Conclusion**

Patients with CRS have significantly elevated levels of nasal mucus glucose concentration that is not influenced by use of topical or systemic steroids. Elevated nasal glucose levels may inhibit the SCC bitter taste receptor–mediated antimicrobial activity and thus blunt local innate antimicrobial defenses.

**Author Contributions**

Kyle M. Hatten, design of work, acquisition, analysis, interpretation, drafting, final approval, accountable for all aspects; James N. Palmer, design of work, acquisition, revising of work, final approval, accountable for all aspects; Robert J. Lee, design of work, revising of work, final approval, accountable for all aspects; Nithin D. Adappa, design of work, revising of work, final approval, accountable for all aspects; David W. Kennedy, design of work, revising of work, final approval, accountable for all aspects; Noam A. Cohen, design of work, analysis, interpretation, drafting/revising, final approval, accountable for all aspects.

**Disclosures**

**Competing interests:** David W. Kennedy, Merck, Medical Advisory Board; ENT ENT care, medical director; Intersect, Sinuwave, consultant; Medtronic, royalties; Accept ENT, partner.

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**References**


