Intranasal steroids and the myth of mucosal atrophy: A systematic review of original histological assessments

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ABSTRACT

Background: *Intranasal corticosteroids (INCSs) are well established in the treatment of allergic rhinitis, chronic rhinosinusitis, and nasal polyposis. Although reversible atrophy of keratinized skin is seen with corticosteroids, the respiratory mucosa is histologically very different and but concerns remain among patients and some health-care professionals over local side effects on nasal respiratory mucosa. A systematic review and meta-analysis were performed of the available evidence for nasal mucosal atrophy as an adverse effect of INCSs in patients with sinonasal disease.*

Methods: *A systematic search of Embase (1974-) and Medline (1946-) databases to September 27, 2013 was performed. Inclusion criteria selected any study where the histopathology of nasal mucosa was assessed in patients with sinonasal disease using intranasally administered corticosteroids with or without a control group.*

Results: *Twenty-three hundred sixty-four publications were retrieved with a subsequent full text review of 149 publications for 34 articles that met the selection criteria. These articles included 11 randomized controlled trials, 5 cohorts, and 20 case series. Duration of treatment varied from 5 days to 5.5 years. "Mucosal atrophy" as an outcome was reported in 17 studies. The definition of "mucosal atrophy" was highly variable with a definition given in only 10 studies. One hundred thirty-six patients were represented in controlled studies of atrophy with only one study reporting the event in both groups with an odds ratio of "mucosal atrophy" at 0.51 (95% CI, 0.09–3.11; p = 0.47).*

Conclusion: *The concept of nasal mucosal atrophy is poorly defined and there is no histological evidence for deleterious effects from INCS use on human nasal mucosa.*

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Intranasal corticosteroids (INCSs) are recommended in the management of rhinitis and chronic rhinosinusitis (CRS), which represent a significant burden of disease and a substantial proportion of primary-care consultations.[1–3] Since their introduction in the 1970s, concerns over systemic and local adverse effects of INCSs have been fuelled partly by adverse effects of oral, inhaled, and potent topical corticosteroids.[4–6] Recent reviews of randomized controlled trials (RCTs) have shown that INCSs, when used appropriately at the recommended dosage, are not associated with adverse effects on the hypothalamic–pituitary axis, bone mineral density, childhood growth rate, glaucoma, cataract, and skin atrophy.[7,8]

Although INCSs have little systemic impact, a clinically relevant concern to patients and some health-care professionals is that using INCSs may cause local damage to the nose.[9–11] Such fears may be confounded by wider use of these medications and case reports of nasal atrophy or septal perforation in patients using older formulations of INCSs, although it remains unclear whether such reports represent clinically relevant adverse effects, examples of corticosteroid allergy, poor applicator technique, preexisting conditions, or natural progression of the underlying disease process.[12–20] Common local adverse effects reported in the literature include epistaxis, throat irritation, nasal dryness, and burning and stinging sensations.[8,21] Such side effects occur in 5–10% of patients using INCSs in RCTs of acute rhinosinusitis,[22] allergic rhinitis (AR),[23] and CRS.[24] With the exception of epistaxis, the incidence of such side effects is similar to placebo and they are mild in severity, usually resolving without discontinuation of treatment.[25–29] Epistaxis leads patients to believe that mucosal damage is occurring.

Recent reviews addressing a limited range of evidence found no mucosal atrophy after prolonged courses of INCSs for sinonasal disease.[8,21] Recent patient surveys reveal concerns about this particular side effect.[9,10,30] This study was designed to provide a systematic and critical appraisal of the available evidence on INCS and mucosal atrophy.

METHODS

Eligibility Criteria

Case series, case–control studies, cohorts, and RCTs were included. Only articles published in English were eligible; reviews, guidelines, letters, case reports, editorials, and *in vitro* and animal studies were excluded. Only studies involving histological measurement of nasal mucosa in patients with sinonasal disease (excluding malignancy) treated with INCSs were included. All reasonable definitions of allergic rhinitis and nonallergic rhinitis (NAR), CRS, and nasal polyposis were included, as were all known formulations and delivery methods of INCSs (see electronic search strategy in the Appendix). Studies with participants of all ages, with any comorbidity and with any duration of treatment and any length of follow-up, were included. Studies that involved the explicit concomitant use of inhaled or systemic corticosteroids or without histological analysis reported were excluded.

Information Sources

The Embase database was searched from 1974 to September 27, 2013, and the Medline database was searched from 1946 to September

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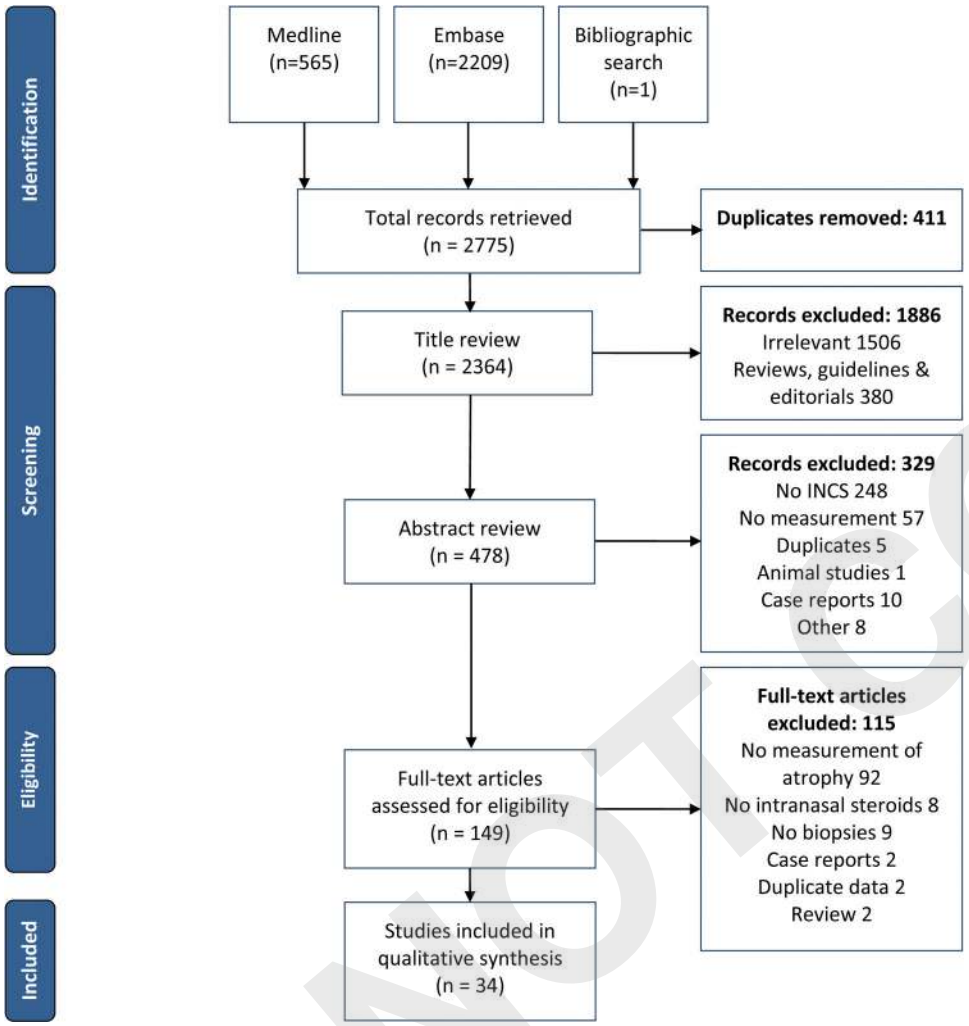

Figure 1. *Study protocol. Based on the PRISMA statement. Source: Reference 74.*

27, 2013, using Ovid SP. Bibliographies of studies selected for full-text analysis were also searched for studies missed by the search strategy. An electronic search strategy (see Appendix) was designed to include all studies concerning the use of INCSs in patients with sinonasal disease where nasal mucosa was assessed.

Study Selection

Study selection was performed by unblinded by two authors (M.M.V. and D.B.) according to predefined selection criteria, and results were reconciled to compile a single group of studies for analysis. The publications retrieved in the initial search were reviewed by title and grouped into those studies containing any reference to sinonasal disease, INCSs, or nasal mucosal atrophy. Remaining studies were subject to abstract review. Studies concerning INCS and sinonasal disease with defined sinonasal groups or those where biopsy specimens of the upper airway were taken were subject to full text analysis.

Data Collection

Data were extracted from the final group of included studies using a standardized data sheet. This was performed independently in duplicate (by authors M.M.V. and D.B.) and all authors reconciled the results. For each study, the following variables were recorded: study type; number of patients; atrophy definitions; exclusion of patients with systemic disease, prior surgery, or exposure to systemic corticosteroids; type, delivery method, dose, frequency, and duration of INCS; tissue biopsy source; sampling method; method of sample analysis; stated outcome measures; and key results. Outcome measures considered relevant to mucosal atrophy were defined as

- Loss of epithelial integrity.
- Epithelial thinning.
- Epithelial ulceration.
- Basement membrane thinning.
- Loss of basement membrane integrity.
- Squamous metaplasia.
- Loss of cilia.
- Change in subepithelial glands.
- Subepithelial fibrosis.
- Loss of goblet cells.
- Increased apoptosis/cell turnover.
- Epithelial edema.

Risk of bias.

Risk of bias in RCTs was assessed at a study level using the Cochrane Risk of Bias Assessment Tool.[31] For cohort studies, risk of bias was assessed in accordance with the Newcastle–Ottawa Scale.[32]

Statistical Analysis

Raw data were extracted from graphs and tables. Odds ratios (ORs) were calculated for dichotomous variables in a fixed-effects model.

Table 1 **Study characteristics—Rhinitis**

Study	Design	Participants	Intervention (*n*)	Comparison (*n*)	Delivery Method	Total Daily Dose	Duration (day)	Biopsy	Anals
Uller *et al.*[75]	RCT*	21 AR	Budesonide (10)	Placebo (11)	Spray	256 μg	6	Turbinate	LM, IHC
Baroody *et al.*[41]	RCT#	51 AR	Fluticasone propionate (26)	Terfenadine (25)	Spray	200 μg	365	Turbinate	LM, TEM
Klossek *et al.*[36]	RCT#	70 AR	A. Triamcinolone acetonide (21); B. beclomethasone dipropionate (26)	Cetirizine (23)	A. Spray; B. spray	A. 220 μg, B. 400 μg, 2. 10 mg	168	Turbinate	LM
Holm *et al.*[51]	RCT*	29 AR	Fluticasone propionate (17)	Placebo (12)	Spray	200 μg	365	Turbinate	LM
Braat *et al.*[76]	RCT*	22 AR	Fluticasone propionate (8)	BKC + placebo (8), Placebo (6)	Spray	200 μg	42	Turbinate	LM, SEM, TEM
Knight *et al.*[43]	A. RCT*; B. case series	A. 11 Mixed rhinitis; B. 9 mixed rhinitis	A. Beclomethasone dipropionate (5); B. beclomethasone dipropionate (9)	A. Placebo (6); B. NA	A. Aerosol; B. aerosol	300 μg	A: 84; B: 252	Turbinate	LM, IHC
Erhan *et al.*[52]	Cohort#	90 NAR	Flunisolide (30)	Silver nitrate (30); saline drops (30)	Spray	200 μg	35	Turbinate	LM
Spector *et al.*[77]	Cohort*	15 AR	Flunisolide (7)	Placebo (8)	Spray	400 μg	28	Turbinate	LM
Poynter *et al.*[53]	A. cohort#; B. case series	A. 10 AR; B. 6 AR	A. Beclomethasone dipropionate (7); B. Beclomethasone dipropionate (6)	A. Placebo (3); B. NA	A. Aerosol; B. aerosol	NR	A. 90–150; B. ≥730	Turbinate	LM
Fokkens *et al.*[30]	Case series	79 AR	A. Fluticasone furoate (37); B. Mometasone furoate (42)	NA	A. Spray; B. spray	A. 110 μg; B. 200 μg	365	Turbinate	LM, IHC
Ozgur *et al.*[72]	Case series	29 AR	Mometasone furoate	NA	Spray	200 μg	21	Turbinate	LM
Can *et al.*[78]	Case series	24 AR	Mometasone furoate + loratadine (12); mometasone furoate (12)	NA	Spray	100 μg	84	Turbinate	LM
Minshall *et al.*[40]	Case series	52 AR	Mometasone furoate (52)	NA	Spray	200 μg	365	Mucosa NOS	LM, IHC
Orgel *et al.*[79]	Case series	48 Mixed rhinitis	Fluocortin butyl	NA	Powder insufflation	2–8 mg	365	Turbinate	LM, IHC
Pipkorn *et al.*[37]	Case series	24 Mixed rhinitis	Budesonide (24)	NA	Aerosol	200 or 400 μg	1095≤ d <2007	Turbinate	LM
Lindqvist *et al.*[80]	Case series	50 Mixed rhinitis	Budesonide (50)	NA	Aerosol	200 or 400 μg	365	Turbinate	LM
Elwany *et al.*[44]	Case series	20 AR	Beclomethasone dipropionate (20)	NA	Aerosol	400 μg	60	Turbinate	TEM
Pipkorn *et al.*[81]	Case series	12 NAR	Budesonide (12)	NA	Aerosol	200 μg (3), 400 μg (9)	365	Turbinate	LM
Balle *et al.*[42]	Case series	15 AR	Budesonide (15)	NA	Aerosol	200–400 μg	300	Mucosa NOS	LM
Sahay *et al.*[82]	Case series	10 AR	Flunisolide (10)	NA	Spray	200 μg	90	Turbinate	LM
Chatterjee *et al.*[34]	Case series	7 AR	Beclomethasone dipropionate (7)	NA	Aerosol	400 μg	90 ≤ d <150	Turbinate	LM

**Double blinding.*
#No blinding.
AR = allergic rhinitis; BKC = benzalkonium chloride; IHC = immunohistochemistry; LM = light microscopy; NA = not applicable; NAR = nonallergic rhinitis; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; SEM = scanning electron microscopy; TEM = transmission electron microscopy.

Table 2 **Study characteristics—CRS**

Study	Design	Participants	Intervention (*n*)	Comparison (*n*)	Delivery Method	Total Daily Dose	Duration, (day)	Biopsy	Analysis
Chang *et al.*[83]	RCT*	48 Mixed CRS	Budesonide (16)	Manuka honey (16), Gentamicin (16)	Merocel sponges	NR	7	Sinus	LM
Molet *et al.*[84]	RCT*	16 CRScNP	Fluticasone propionate (8)	Placebo (8)	Spray	400 μg	28	Polypectomy/ turbinate (control)	IHC
Holopainen *et al.*[45]	RCT*	16 NP	Budesonide (8)	Placebo (8)	Spray	400 μg	120	Polyp biopsy	LM
Klemi *et al.*[46]	RCT*	37 Post-ethmoidectomy	Beclomethasone dipropionate (22)	Placebo (15)	Powder insufflator	400 μg	365	Turbinate	LM
Saunders *et al.*[85]	RCT*	22 NP	Fluticasone propionate (11)	Placebo (11)	Spray	NR	14	Polypectomy specimen	LM, IHC, TEM
Alatas *et al.*[47]	Cohort#	29 NP	Fluticasone propionate(16)	No treatment (13)	NR	NR	d ≥90	Polyp biopsy	LM
Drvis *et al.*[48]	Case series	30 CRSsNP	Dexamethasone (30)	NA	Maxillary antrostomy tube	2 mg	5	Sinus	LM
Mastruzzo *et al.*[86]	Case series	10 NP	Budesonide (10), Mygind	NA	Powder insufflator	400 μg	56	Polypectomy/ turbinate (control)	LM, IHC
Lacroix *et al.*[87]	Case series	50 NP	Corticosteroid NOS (50)	NA	Spray	400 mg	d ≥180	Polypectomy specimen	LM
Mygind *et al.*[38]	Case series	33 NP	Beclomethasone dipropionate (33)	NA	Aerosol	400 μg	270≤ d <1080	Polyp biopsy	LM, SEM
Sorensen *et al.*[39]	Case series	33 NP	Beclomethasone dipropionate (33)	NA	Aerosol	400 μg	270≤ d <365	Polyp biopsy	LM, SEM, Cyt

**Double blinding.*
#No blinding.
CRS = chronic rhinosinusitis; CRScNP = chronic rhinosinusitis with nasal polyps; Cyt = cytology; IHC = immunohistochemistry; LM = light microscopy; NA = not applicable; NP = nasal polyposis; NOS = not otherwise specified; NR = not reported; RCT = randomized controlled trial; SEM = scanning electron microscopy; TEM = transmission electron microscopy.

Table 3. **Study characteristics—Mixed rhinitis/CRS**

Study	Design	Participants	Intervention (*n*)	Comparison (*n*)	Delivery Method	Total Daily Dose	Duration (day)	Biopsy	Analysis
Bende *et al.*[50]	Cohort#	21 Mixed nasal polyposis/AR	Beclomethasone dipropionate dipropionate or budesonide or both (11)	No treatment (10)	NR	NR	60≤ d <1080	Septum	LM
Holopainen *et al.*[49]	Case series	23 Mixed rhinitis + nasal polyposis	Beclomethasone dipropionate (23)	NA	Spray	0–400 μg/d	365≤ d <1825	Mucosa NOS	LM

#*No blinding.*
AR = allergic rhinitis; CRS = chronic rhinosinusitis; LM = light microscopy; NA = not applicable; NOS = not otherwise specified; NR = not reported.

For continuous data, mean differences were calculated from baseline and final means and SD of change using an inverse variance, fixed-effect model with 95% CIs (Review Manager [RevMan] Version 5.2., Copenhagen, The Nordic Cochrane Center, The Cochrane Collaboration, 2012). Where SDs of change were not available, this was imputed from baseline and final means as described in the Cochrane Handbook.[33] Forest plots were visually inspected to investigate statistical heterogeneity. Heterogeneity between studies was assessed clinically for each study and investigated using the I^2 statistic, which provides an estimate of the percentage of variation observed in results that is unlikely to be due to chance. A value of ≥50% was taken to indicate heterogeneity.

RESULTS

A total of 2774 articles were retrieved. One publication was added from bibliographic searching of an included article.[34] After removal of duplicates, 2364 publications remained. A systematic review of titles, abstracts, and full-text publications was performed, as described in Fig. 1. Two publications reported the same data from the same patients and therefore were treated as one study.[35,36] A total of 34 publications remained for data extraction (see Fig. 1). Some publications reported more than 1 study, so a total of 36 clinical studies (from 34 publications) were analyzed.

The characteristics of the included studies are shown in Tables 1–3. Demographic details and efforts to control confounding were incompletely reported. Eleven RCTs, 5 prospective cohort studies, and 20 case series were included. The final group of studies included 23 studies on patients with rhinitis, 11 studies on patients with CRS, and 2 studies that assessed a mixed cohort of patients with rhinitis and nasal polyposis.

In the 16 controlled trials, 251 patients received INCSs and 266 patients received placebo or non-INCS medications. In the case series, 564 patients received INCSs.

Study Objectives

The aims of included studies were variable, ranging from the assessment of long-term safety and efficacy to specific aims to examine the effects of INCSs on histological appearances of nasal mucosa. Seventeen included studies explicitly mentioned nasal mucosal atrophy in the body of the article.

Definitions of Atrophy

The histological features that were taken to characterize mucosal atrophy varied among the studies that included a definition of this pathology (Table 4). A total of 7/17 studies that mentioned mucosal atrophy did not provide a definition. The remaining definitions varied from the presence of squamous metaplasia alone[36–39] to compound definitions encompassing thinning of the epithelial and collagen layers, increase in tissue edema, and increased regularity of collagen fibrils.[40,41]

Interventions

Several INCSs were subject to investigation, with some studies investigating more than one agent (Tables 1–3). Duration of treatment also varied considerably from 5 days to 5.5 years (Tables 1–3).

Methods of Sampling and Analysis

Biopsy specimens of nasal mucosa were taken in a clinic setting in 26 studies, and surgical specimens were used in 9 studies. In 20 studies, tissue from turbinate biopsy was used for analysis, with the remaining studies analyzing tissue from sinus, septum, unspecified nasal mucosa, nasal polyp biopsy, and polypectomy specimens. Thirty-five studies used light microscopy for sample analysis, with 9 studies using immunohistochemistry, 4 studies using transmission electron microscopy, and 3 studies using scanning electron microscopy.

Table 4 **Atrophy-related definitions and outcomes**

Study	Population	Atrophy Definition	Atrophy-related Outcome Measures
Fokkens *et al.*[30] 2012	AR	Epithelial thinning	Epithelial thickness (ratio of epithelial cross-sectional area to BM length)
			Epithelial phenotype (% of epithelium composed of: BM only; BM + basal cells; BM + basal cells + dissociated columnar cells; BM+ basal cells + intact columnar cells; intact epithelium inc. cilia)
			Percent ratio of goblet cells to epithelial cells
Ozgur *et al.*[72] 2011	AR	NA	Goblet cells in nasal brushings, percent of epithelial cell count, ordinal scale
Uller *et al.*[75] 2010	AR	NA	Total apoptotic cells/mm^2
			Ki-67+ cells/0.1 millimeter BM
Can *et al.*[78] 2006	AR	Epithelial or BM thinning	Squamous metaplasia nominal scale (absent/focal/diffuse)
			Thickness of BM (μm, median of 5 measurements)
			Thickness of epithelium (μm, median of 5 measurements)
Baroody *et al.*[41] 2001.	AR	Any of (i) epithelial thinning; (ii) reduction collagen layer thickness; (iii) increase in edema; (iv) increase in regularity of collagen fibrils	Epithelium layer thickness (μm, mean of 3 measurements on LM)
			Collagen layer thickness (μm, mean of 5 measurements on LM)
			Presence of edema (4-point ordinal scale, EM)
			Regularity of collagen fibrils (3-point ordinal scale, EM)
Klossek* *et al.*[36] 2001	AR	Squamous metaplasia	Nasal mucosal epithelium thickness (μm, ratio of area to length)
			Appearance of mucosal epithelium
Holm *et al.*[51] 1998	AR	"Atrophy," not otherwise defined	Four-point ordinal scale (details not published):
			Appearance of epithelial layer
			Degree of tissue edema
Minshall *et al.*[40] 1998	AR	Any of: (i) reduction in epithelial thickness; (ii) reduction in ratio of epithelial cross-sectional area to length of BM; (iii) squamous metaplasia.	Thickness of the epithelium (mean, mm)
			Ratio of epithelial cross sectional area to BM length
			Percentage of ciliated intact epithelium.
			Qualitative comments on: epithelial type and integrity; abundance of goblet cells; presence of focal metaplasia; BM structure; lamina propria morphology; morphology of vessels and glands.
Erhan *et al.*[52] 1996	NAR	NA	Mucosal epithelium cell type, BM thickness, edema, inflammation (nominal scale)
			Eosinophil count, ordinal scale
Braat *et al.*[76] 1995	AR	NA	SEM: Subjectively assessed ratio of ciliated/nonciliated cells per hpf
			LM: epithelial cells/μm; edema (ordinal scale)
			TEM: Non-quantified examination of epithelial ultrastructure (mitochondria, cilia, ER)
			Number or damage to cilliated cells on LM or EM.
Orgel *et al.*[79] 1991	Mixed rhinitis	Squamous metaplasia	Type of epithelium, nominal scale
			Thickness of BM, nominal scale
			Number of glands per hpf
Pipkorn *et al.*[37] 1988	Mixed rhinitis	Squamous metaplasia and BM thinning	Nominal scales (3-point): epithelial metaplasia; number of goblet cells per hpf; thickness of basal membrane
Lindqvist *et al.*[80] 1986	Mixed rhinitis	"Atrophy," not otherwise defined	Epithelial metaplasia (nominal scale)
			Number of goblet cells (nominal scale)
			Thickness of basal membrane (nominal scale)
Elwany *et al.*[44] 1983	AR	NA	Qualitative changes in EM appearances compared to baseline
Knight *et al.*[43] 1983	Mixed rhinitis	"Atrophy," not otherwise defined	Presence/absence of BM thickening or squamous metaplasia
Pipkorn *et al.*[81] 1983	NAR	NA	Four-point ordinal scale: squamous epithelium; number of goblet cells; thickening of the basal lamina
Balle *et al.*[42] 1982	AR	NA	Semiquantitative measurement of epithelial metaplasia (details not published)
Sahay *et al.*[82] 1980	AR	"Atrophy," not otherwise defined	Type of surface epithelium, nominal scale
			Ordinal scale: BM thickness, number of submucous glands, degree of edema, fibrosis.

Table 4 **Continued**

Study	Population	Atrophy definition	Atrophy-related Outcome Measures
Spector *et al.*[77] 1980	AR	NA	BM appearance, nominal scale
			Degree of edema, ordinal scale
Chatterjee *et al.*[34] 1977	AR	NA	Qualitative: Appearances of epithelium, BM, edema, eosinophilia, collagen
Poynter *et al.*[53] 1977	AR	NA	Qualitative description of epithelium
			BM thickness, nominal scale
			Presence/absence of edema
			Collagenous fibres (normal/abundant)
Chang *et al.*[83] 2011	Mixed CRS	NA	
Alatas *et al.*[47] 2006	NP, ACP	NA	Presence/absence: Squamous metaplasia, epithelial damage (defined as surface epithelial hyperplasia, epithelial desquamation, and BM rupture), edema, fibroblastic density, stromal hyalinization and glandular hyperplasia.
Drvis *et al.*[48] 2004	CRSsNP	NA	Four-point ordinal scale:
			Number of inflammatory cells
			Edema
			Fibrosis
			Seromucous glands
			Goblet cell density
Mastruzzo *et al.*[86] 2003	Nasal polyposis	NA	Epithelial damage - % of damaged epithelium on 4-point ordinal scale
			Presence/absence ciliated cells
Molet *et al.*[84] 2003	CRScNP	NA	Mean cell count per hpf (type V collagen)
			Nominal score for type I + III collagen deposition (staining intensity, extent of collagen deposition, BM thickness)
Lacroix *et al.*[87] 2002	Nasal polyposis	NA	Integrity of epithelium (details not given)
			Presence/absence edema,
Saunders *et al.*[85] 1999	Nasal polyposis	NA	Percent of apoptotic/mitotic cells per hpf in epithelium and stroma
			Percent of Ki67+ cells per hpf in epithelium and stroma
Holopainen, Grahne *et al.*[45] 1982	Nasal polyposis	"Atrophy," not otherwise defined	Qualitative description of epithelial degeneration, metaplasia & mucosal atrophy
Klemi *et al.*[46] 1980	Postethmoidectomy	"Atrophy," not otherwise defined	Qualitative comments on:
			Quality of epithelium
			Thickness of basal membrane
			Edema of lamina propria
			Presence of mucous glands
			Presence of fibrosis
Mygind *et al.*[38] 1978	Nasal polyposis	Squamous metaplasia	Tissue edema, 3-point ordinal scale
			Goblet cells per mm epithelium
			Surface epithelium type on LM, ordinal scale (0–100, squamous to pseudostratified)
			Surface epithelium type on SEM, ordinal scale (0–100)
Sorensen *et al.*[39] 1976	Nasal polyposis	Squamous metaplasia	Semiquantitative appearances of polyp tissue on LM (details not reported)
			Category of epithelium on SEM, nominal scale
Bende *et al.*[50] 1992	Mixed nasal polyposis/ AR	Squamous metaplasia or BM thinning	Thickness of basal membrane (7-point ordinal scale)
			Fibrosis (7-point ordinal scale)
			Squamous metaplasia (±)
Holopainen, Malmberg *et al.*[49] 1982	Mixed rhinitis + nasal polyposis	"Atrophy," not otherwise defined	Epithelial metaplasia, nominal scale
			"Atrophy," not quantified ?binary outcome

TEM = transmission electron micoroscopy; LM = light microscopy; BM = basement membrane; EM = electron microscopy; ER = endoplasmic reticulum; AR = allergic rhinitis; CRS = chronic rhinosinusitis; CRScNP = chronic rhinosinusitis with nasal polyps; NA = not applicable; NAR = nonallergic rhinitis; SEM = scanning electron microscopy; CRSsNP = chronic rhinosinusitis without nasal polyps; ACP = antrochoanal polyp; hpf = high powered field.

Table 5 **Atrophy outcomes—Noncontrolled studies only**

Study	Population	Atrophy Outcomes												Summary
		Epithelial Integrity Loss	Epithelial Thinning	Ulceration	BM Thinning	BM Integrity Loss	Squamous Metaplasia	Loss of Cilia	Change in Subepithelial Glands	Subepithelial Fibrosis	Loss of Goblet Cells	Increased Apoptosis/ Cell Turnover	Edema	
Fokkens *et al.*[30] 2012	AR	Absent	Absent	NR	NR	NR	NR	Absent	NR	NR	Absent	NR	NR	Epithelial thickness: mm, mean change from baseline (±SD): fluticasone: −0.008 (0.019); mometasone: −0.006 (0.018). % Goblet cells in biopsies (mean change from baseline ±SD): Fluticasone −2.1 (10.44); Mometasone 0.7 (10.63); % epithelium BM only: Mean change from baseline ±SD: Fluticasone −0.662 (4.5452); Mometasone 1.926 (16.1207). % intact ciliated cells: Mean change from baseline ±SD: Fluticasone: 9.183 (42.3472); Mometasone 2.878 (40.8399).
Ozgur *et al.*[72] 2011	AR	NR	NR	NR	NR	NR	NR	NR	NR	NR	Present	NR	NR	Goblet cell cytology ordinal score (pre-INCS vs post-INCS, mean ± SD): 0.83 ± 0.92 vs 0.17 ± 0.46 $p = 0.001$
Can *et al.*[78] 2006	AR	NR	Absent	NR	Absent	NR	Absent	NR	NR	NR	NR	NR	NR	Quantitative data not published. Squamous metaplasia: Decreased with treatment with mometasone + loratadine ($p < 0.05$) but not INCS alone. BM thickness: No change from baseline ($p > 0.05$) Epithelium thickness: No change from baseline ($p > 0.05$)
Minshall *et al.*[40] 1998	AR	Absent	Absent	NR	NR	Absent	Absent	NR	Absent	NR	Absent	NR	NR	Epithelial thickness (mm, mean ±SEM): INCS: 0.053 (0.003) vs 0.052 (0.003), $p > 0.05$, pre-INCS vs post-INCS; Ratio of cross-sectional area to length of BM, ratio ±SEM: INCS: 0.046 (0.002), 0.045 (0.002) $p > 0.05$; % ciliated cells: 59% vs 71%, pre-INCS vs post-INCS, NS, Intact epithelium: 21.6% vs 29.4%, pre-INCS vs post-INCS, NS. Squamous metaplasia: 11.8% vs 7.8%, pre-INCS vs post-INCS, NS. No change in integrity of BM post-INCS (data not given), No change in distribution or density of goblet cells (data not given) No change in morphological features of vessels and glands in lamina propria (data not given)
Orgel *et al.*[79] 1991	Mixed rhinitis	NR	NR	NR	Absent	Absent	Absent	NR	NR	NR	NR	NR	NR	Epithelial metaplasia (No. of biopsies, $n = 40$, pre-INCS vs post INCS): Columnar: 15 vs 28; cuboidal 12 vs 6; Squamous 13 vs 6, BM quality (no. of biopsies, $n = 41$), pre-INCS vs post-INCS: Thinning: 15 vs 12; Partial destruction: 4 vs 6; Complete destruction: 3 vs 2; Normal 17 vs 21; not in sample 2 vs 0, No of glands: mentioned in methods, not in results
Pipkorn *et al.*[37] 1988	Mixed rhinitis	NR	NR	NR	Absent	NR	Absent	NR	NR	NR	Absent	NR	NR	No statistical analysis reported. No statistically significant change in epithelial metaplasia, BM thickness or goblet cells. No. of biopsies ($n = 10$), data post-INCS only, increase vs no change vs decrease: Epithelial metaplasia: 4 vs 4 vs 2, BM thickness: 2 vs 7 vs 1, Goblet cell no.: 0 vs 9 vs 1
Lindqvist *et al.*[80] 1986	Mixed rhinitis	NR	NR	NR	Absent	NR	Absent	NR	NR	NR	Absent	NR	NR	Data are no. of biopsies, Epithelial metaplasia: 10/40 increase, 22/40 no change, 8/40 decrease, $p = 0.81$, BM thickness: 7/39 increase, 27/39 no change, 5/39 decrease, $p = 0.77$, Goblet cells: 11/39 increase, 18/39 no change, 10/39 decrease, $p = 1.00$
Elwany *et al.*[44] 1983	AR	NR	NR	NR	NR	NR	NR	Absent	Present	NR	Present	NR	Absent	No quantitative data.
Knight *et al.*[43] 1983 (B)	Mixed rhinitis	NR	NR	NR	Absent	NR	Present	NR	NR	NR	NR	NR	NR	Data are no. of biopsies, Squamous metaplasia: 4/16 vs 5/9, Baseline vs 48 weeks INCS, BM "thickening", not defined: 13/16 vs 7/9, baseline vs 48 weeks INCS. No evidence of mucosal atrophy (details not given).

Table 5 **Continued**

Study	Population	Atrophy Outcomes												Summary
		Epithelial Integrity Loss	Epithelial Thinning	Ulceration	BM Thinning	BM Integrity Loss	Squamous Metaplasia	Loss of Cilia	Change in Subepithelial Glands	Subepithelial Fibrosis	Loss of Goblet Cells	Increased Apoptosis/ Cell Turnover	Edema	
Pipkorn *et al.*[81] 1983	NAR	NR	NR	Absent	NR	Absent	NR	NR	NR	Absent	NR	NR	NR	No statistical analysis. Squamous epithelium (any degree, no. of biopsies): 3/9 vs 5/12, pre-INCS vs post-INCS, Presence of goblet cells (any degree, no. of biopsies): 6/9 vs 10/12, pre-INCS vs post-INCS, BM thickening (any degree, no. of biopsies) 11/12 vs 12/12, pre-INCS vs post-INCS
Balle *et al.*[42] 1982	AR	NR	NR	NR	NR	NR	Present	NR	NR	NR	NR	NR	NR	Tendency towards increased metaplasia with duration of INCS treatment (graphical data only).
Sahay *et al.*[82] 1980	AR	NR	NR	NR	Absent	NR	Absent	NR	Absent	Absent	NR	NR	Absent	No statistical analysis. Data are no. of biopsies, Squamous metaplasia (any degree, no. of biopsies): 5/10 vs 5/10, BM thickening: None seen, Glands: 3/10 cases increased number of glands, 0/10 decrease, 7/10 stayed same, Oedema:5/10 vs 4/10 pre-INCS vs post-INCS, Fibrosis: 3/10 vs 3/10 pre-INCS vs post-INCS
Chatterjee *et al.*[34] 1977	AR	NR	NR	NR	Absent	NR	NR	NR	NR	NR	NR	NR	Absent	Data are no. of biopsies, Oedema: 5/6 vs 0/6, baseline vs post INCS, No changes seen in the epithelium or BM. BM remained thickened pre and post INCS. Collagenous structures of lamina propria "normal"
Poynter *et al.*[53] 1977 (B)	AR	NR	NR	NR	Absent	NR	Absent	NR	Absent	Absent	NR	NR	Absent	Data for 2 yr + INCS: No pretreatment biopsy data, Squamous changes: 3/6 biopsies, Oedema: 4/6 biopsies, Hyperplasia of subepithelial glands: 1/6, BM thinning: 0/6
Drvis *et al.*[48] 2004	CRSsNP	NR	NR	NR	NR	NR	NR	NR	Absent	Absent	Absent	NR	Absent	No quantitative data published. No statistical difference reported in edema, fibrosis, number of seromucous glands or goblet cell density).
Mastruzzo *et al.*[86] 2003	Nasal polyposis	Absent	NR	NR	NR	NR	NR	NR	NR	Absent	NR	NR	NR	Only graphical data. Improvement in markers of epithelial damage seen after INCS (ordinal scale). No macroscopic differences in collagen staining or distribution (data not given)
Lacroix *et al.*[87] 2002	Nasal polyposis	NR	NR	Absent	Absent	NR	NR	NR	NR	NR	NR	NR	NR	Data are % of biopsies. Ulceration: 20% vs 10% vs 10%, African (no INCS), Chinese (no INCS) vs Caucasian (INCS). No significant BM thickening (data not given)
Mygind *et al.*[38] 1978	Nasal polyposis	NR	NR	NR	Absent	NR	Absent	Absent	Absent	NR	Present	NR	Absent	No change in BM thickness (no quantitative data), No change in subepithelial glands (no quantitative data), edema decreased with INCS (2.4 vs 1.6, mean of ordinal score, $p < 0.05$), Goblet cells decreased ($p < 0.01$), only graphical data, No consistent tendency towards squamous metaplasia
Sorensen *et al.*[39] 1976	Nasal polyposis	NR	NR	NR	NR	NR	Absent	NR	NR	NR	NR	NR	NR	No quantitative data given. LM: No change seen in distribution of pseudostratified, ciliated and squamous epithelium. SEM: No tendency towards respiratory or squamous epithelium observed during INCS treatment
Holopainen, Malmberg *et al.*[49] 1982	Mixed rhinitis/ nasal polyposis	NR	NR	NR	NR	NR	Present	NR	NR	NR	NR	NR	NR	Data are no. of biopsies, Metaplasia after 2 yr: 6/17 vs 9/17, pre-INCS vs post-INCS, Metaplasia after 6 yr: 4/6 on INCS

BM = basement membrane; NR = not reported; NS = not significant; LM = light microscope; SEM = scanning electron microscope; AR = allergic rhinitis; CRScNP = chronic rhinosinusitis with nasal polyps; INCS = intranasal corticosteroid; SD = standard deviation.

Table 6 **Results—Controlled studies only**

Author	Yr	Design	*n*	Population	INCS (*n*)	Evidence of "Atropy" (*n*) or % or Baseline, Post, or Change Scale Data	Non INCS (*n*)	Evidence of "Atropy" (*n*) or % or Baseline, Post or Change Scale Data
Uller *et al.*[75]	2010	RCT	21	AR	10	Total apoptotic cells (TUNEL +ve/mm^2, mean ± SEM): placebo vs INCS, decreased with INCS, $p < 0.05$ (graphical data)	11	see INCS column
Baroody *et al.*[41]	2001	RCT	51	AR	26 (max)	All data as Mean (±SE), baseline vs study end, epithelium thickness BM (μm): 27.77 (4.97) vs 35.17 (5.14), $p = 0.37$, $n = 25$ ($p < 0.05$ vs non-INCS), collagen thickness/BM (μm): 11.45 (0.58) vs 11.97(0.84), $p = 0.68$, $n = 26$, Lucent spaces ordinal score (edema) 1.19 (0.15) vs 1.05 (0.18), NS (p not given), $n = 21$, regularity of collagen fibrils score, 1.83 (0.16) vs 2.05 (0.14), NS, $n = 20$	25 (max)	All data as mean (±SE), change scale data (baseline vs study end), epithelium thickness (μm): 28.55 (4.27) vs 20.91 (2.50), $p = 0.23$, $n = 21$ $p < 0.05$ vs non-INCS), collagen thickness/BM (μm): 11.71 (0.87) vs 12.46 (0.87), $p = 0.47$, $n = 25$, Lucent spaces ordinal score (edema), 1.09 (0.15) vs 1.14 (0.17), NS (p not given), $n = 22$, regularity of collagen fibrils score, 1.75 (0.14) vs 1.85 (0.11), NS, $n = 20$
Klossek *et al.*[36]	2001	RCT	70	AR	A. 21, B. 26	Mucosal thickness (total epithelium + BM, μm change from baseline, mean ±SE): A. TAA: −9.1 (6.8) $n = 21$, B. BDP, −6.0 (7.6) $n = 26$, $p = 0.95$ between groups. BM thickness (μm change from baseline, mean ±SE): A.TAA 1.7(1.1), $n = 21$, B: BDP −1.0(0.9) $n = 26$, $p = 0.1$ between groups. No change in squamous metaplasia, data not given, No epithelial destruction, data, not given	23	Mucosal thickness (total epithelium + BM, μm change from baseline, mean ±SE): Cetirizine −8.2 (6.7), $p = 0.95$ between groups. BM thickness (μm change from baseline, mean ±SE): Cetirizine −0.3 (-0.7), $p = 0.1$ between groups. No change in squamous metaplasia, data not given, No epithelial destruction, data not given
Holm *et al.*[51]	1998	RCT	29	AR	17	All data are mean scores from 4-point ordinal scale. pre-INCS vs post INCS, edema: 0.8 vs 0.7, NS, BM thickening: 0.6 vs 0.8, NS, "Epithelial damage" NOS, 1 vs 0.7, NS	12	All data are mean scores from 4-point ordinal scale, pre-INCS vs post INCS. Oedema: 0.8 vs 0.8, NS, BM thickening: 0.9 vs 0.7, NS, "Epithelial damage" NOS, 1.2 vs 1.1 NS
Braat *et al.*[76]	1995	RCT	22	AR	8	Edema: No significant change in ordinal score of edema between groups on LM ($p = 0.627$), Ciliated cells: no significant change in ciliated cell counts between groups on LM ($p = 0.46$). Cilia appear similar in most specimens on TEM. No INCS-specific data from SEM	14	See INCS column
Knight *et al.*[43] (A)	1983	RCT	11	Mixed rhinitis	5	Obvious BM thickening in most baseline biopsies, no change at 12 wk. (no data), Squamous metaplasia found at baseline and 12 weeks (no data)	6	See INCS column
Erhan *et al.*[52]	1996	Cohort	90	NAR	30 (max)	Data as % biopsies post-treatment, Squamous epithelium: INCS 33% (9/27), BM thinned: INCS 20% (6/30), BM eroded: INCS 37% (11/30), Severe edema: INCS 30% (7/23), Reported as no statistically significant difference between any outcome, INCS vs no INCS $p > 0.05$.	60 (max)	Data as % biopsies post-treatment, Squamous epithelium, Saline: 89% (25/28), Silver nitrate: 24% (7/29), BM thinned: Saline: 33% (10/30), Silver nitrate: 10% (3/30), BM eroded: Saline 67% (20/30), Silver nitrate 20% (6/30), Severe edema: Saline: 63% (19/22), Silver nitrate: 16% (4/25), Reported as no statistically significant difference between any outcome, INCS vs no INCS $p > 0.05$.
Spector *et al.*[77]	1980	Cohort	15	AR	7	No. of biopsies (pre-INCS vs post-INCS), Squamous epithelium: 4/7 vs 3/7, BM intact, 6/7 vs 6/7, edema (mean ordinal score), 0.93 vs 0.57	8	No. of biopsies (pre-INCS vs post-INCS): Squamous epithelium: 8/8 vs 8/8, BM intact, 2/7 vs 2/7, edema (mean ordinal score), 0.38 vs 0.94
Poynter *et al.*[53] (A)	1977	Cohort	10	AR	7	No stats. Data as no. of biopsies pre and post 3 months treatment, Squamous changes: 1/7 vs 2/7, pre-INCS vs post-INCS, BM thinning: 0/7 vs 0/7; pre-INCS vs post-INCS, edema: 6/7 vs 1/7, pre-INCS vs post-INCS, Change in collagenous fibres: 7/7 "normal" vs 6/7 "normal", 1 "abundant",	3	No stats. Data as no. of biopsies pre vs post 3 month treatment, Squamous changes: 1/3 vs 2/3, BM thinning: 3/3 "thick BM" vs 2/3 "thick", 1 "normal", edema: 3/3 vs 1/3, Collagenous fibres: 3/3 "normal" vs 2/3 "normal", 1 "abundant"
Chang *et al.*[83]	2011	RCT	48	Mixed CRS	16	No change in mucosal inflammation/tissue necrosis between groups (5-point nominal scale)	32	see INCS column
Molet *et al.*[84]	2003	RCT	16	CRS	8	Incomplete reporting, No data given, only p values. No. of type I, III or V collagen-expressing cells (pre-INCS vs post-INCS) ($p = 0.83$, $p = 0.63$, $p = 0.86$ respectively vs baseline);, Number of type I, III or V expressing cells: $p = 0.06$ (INCS vs placebo for type V only), (Increased collagen I, III and V in NPs vs control at baseline only; $p = 0.02$, $p = 0.002$, $p = 0.001$ respectively)	8	Incomplete reporting, Number of type I, III or V expressing cells: $p = 0.06$ (INCS vs placebo for type V only)
Holopainen, Grahne *et al.*[45]	1982	RCT	16	Nasal polyposis	8	Data are no. of biopsies, Epithelial (squamous) metaplasia: 1/8 vs 0/8, pre-INCS vs post-INCS, Atrophy: No biopsies	8	Data are no. of biopsies, Epithelial (squamous) metaplasia:2/8 vs 0/8 pre- and post-solvent only), Atrophy: No biopsies
Klemi *et al.*[46]	1980	RCT	37	CRS, Post ethmoidectomy	22	Data are no. of biopsies, Squamous metaplasia: 2/22 vs 8/22, pre-INCS vs post-INCS, No change in BM thickness (data not given), Change in oedema after treatment: 35% (8/22) patients decreased, 64% (14/22) no change, 0% increased.	15	Data are no. of biopsies, Squamous metaplasia: 3/15 vs 5/15, pre vs post, No change in BM thickness (data not given), Change in oedema after treatment: 13% (2/15) decreased; 73% (11/15) no change, 13% (2/15) increased

Table 6 **Continued**

Author	Yr	Design	*n*	Population	INCS (*n*)	Evidence of "Atropy" (*n*) or % or Baseline, Post, or Change Scale Data	Non INCS (*n*)	Evidence of "Atropy" (*n*) or % or Baseline, Post or Change Scale Data
Saunders[85]	1980	RCT	22	Nasal polyposis	11	Data not always given. *P* values are INCS vs placebo, Apoptotic index (% apoptotic cells, stroma), $p = 0.61$, Apoptotic index (% apoptotic cell, epithelium), $p = 0.72$, Mitotic index (% mitotic cells, stroma), $p = 0.89$, Mitotic index (% mitotic cells, epithelium, median ± SE): 0.16(0.08) vs 0.38(0.08), INCS vs placebo, $p = 0.06$, Apoptotic index/Mitotic index ratio (epithelium,median ± SE): 4.34(0.6) vs 2.12(0.6), $p = 0.018$, Ki-67 cell count (stroma, median ± SE); $p = 0.98$, Ki-67 cell count (epithelium, median ± SE), 12.7(1.7) vs 8.5(1.7), $p = 0.092$	11	see INCS column
Alatas *et al.*[47]	2006	Cohort	29	Nasal polyposis, antrochoanal polyps	16 (max)	All data as % of biopsies post treatment, *p* values compare INCS vs no treatment, Epithelial damage: 0% $p = 0.412$ (non-allergic NPs, $n = 10$), 0% $p = 0.036$ ("allergic NPs", $n = 6$), Squamous metaplasia: 0% $p = 0.065$ (non-allergic);. 0% $p = 0.036$ (allergic NPs), Fibrosis: 0% $p = 0.065$ (non-allergic); 66.7% $p = 0.455$ (allergic NPs), Edema: 80% $p = 1.0$ (non-allergic); 33.3% $p = 0.061$ (allergic), Ki-67+ cells: 0% $p = 0.055$ (non-allergic); 33.3% $p = 0.061$ (allergic), Glandular hyperplasia: 100% $p = 0.055$ (non-allergic); 100% $p = 0.038$ (allergic)	13 (max)	% of biopsies pre treatment, only, combined with pre-treatment INCS group *p* values compare INCS vs no treatment, Epithelial damage: 14.3%, $p = 0.412$ (non-allergic NPs);. 100% $p = 0.036$ (allergic NPs), Squamous metaplasia: 42.9%, $p = 0.065$ (non-allergic. $n = 8$);. 100% $p = 0.036$ (allergic NPs, $n = 5$), Fibrosis: 42.9%, $p = 0.065$ (non-allergic); 100%, $p = 0.455$ (allergic NPs), Edema: 71.4%, $p = 1.0$ (non-allergic); 100% $p = 0.061$ (allergic), Ki-67+ cells: 57.1%, $p = 0.055$ (non-allergic); 100%, $p = 0.061$ (allergic), Glandular hyperplasia: .9%, $p = 0.055$ (non-allergic); 10%, $p = 0.038$ (allergic)
Bende *et al.*[50]	1992	Cohort	21	Mixed nasal polyposis, /AR	11	All data as Mean of ordinal score (±SD), INCS vs No treatment, BM thickness: 3.0(1.6), NS, Fibrosis: 2.5(1.4), NS, Numbers of biopsies post treatment, Epithelial metaplasia: 6/11, NS	10	All data as Mean of ordinal score (±SD), INCS vs No treatment, BM thickness: 2.7(1.7), NS, Fibrosis: 2.8(1.4), NS, Numbers of biopsies post treatment, Epithelial metaplasia: 7/10, NS

AR = allergic rhinitis; BDP = budesonide propionate aerosol; BM = basement membrane; CRS = chronic rhinosinusitis; TAA = triamcinolone acetonide; TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling; SE = standard error; INCS = intranasal corticosteroid; BM = basement membrane; LM = light microscopy; NS = not significant; NP = nasal polyposis; NOS = not otherwise specified; NAR = nonallergic rhinitis; RCT = randomized controlled trial; SEM = scanning electron microscopy; TEM = transmission electron microscopy.

Measurement of Atrophy Outcomes

There were no standardized methods for measuring mucosal atrophy across the studies. Epithelial or basement membrane thickness was reported variably as one measurement, the mean or median of several measurements, the ratio of epithelial cross-sectional area to basement membrane length, or qualitatively on an ordinal or nominal scale (Table 4).

Rhinitis

The results are summarized in Tables 5 and 6. None of the 11 studies (RCTs, cohorts, or case series) that included atrophy as an outcome reported atrophy in nasal mucosal biopsy specimens from patients with rhinitis using INCSs. In controlled studies measuring epithelial or basement membrane thinning, squamous metaplasia, loss of cilia, fibrosis, increased apoptosis, or mucosal edema, no studies reported significant changes in these outcomes among users of INCSs compared with patients receiving placebo or non-INCS medications (Table 6). Squamous metaplasia was seen in 2/9 case series that reported this outcome in patients with rhinitis using INCSs.[42,43] One case series reported a qualitative finding of loss of goblet cells and a change in subepithelial glands in patients with AR using beclomethasone dipropionate aerosol,[44] although these outcomes were not investigated in control subjects.

Chronic Rhinosinusitis

Two controlled studies[45,46] and two case series[38,39] of CRS patients included atrophy as an outcome. No studies reported atrophy in nasal mucosal biopsy specimens from patients with CRS using INCSs (Table 6). One cohort study found significant improvements in epithelial integrity and squamous metaplasia but increased glandular hyperplasia in the INCS group relative to baseline biopsy specimens of control patients.[47] Three case series measured loss of goblet cells,[38,40,48] with Mygind *et al.* reporting a significant loss among users of beclomethasone dipropionate aerosol compared with baseline, although this outcome was not investigated in control subjects.

Two studies investigated a mixed population of rhinitis/CRS patients (Tables 5 and 6). The finding of squamous metaplasia in a case series of patients using INCSs[49] was not replicated in a controlled study that reported no significant changes in basement membrane thickness, fibrosis, or squamous metaplasia between patients receiving INCSs and those on no treatment.[50]

Meta-Analysis

For those controlled studies declaring an outcome of "mucosal atrophy," 136 patients on INCSs were compared with 99 of the control arm.[36,41,43,45,46,50,51] The OR for the chance of developing mucosa atrophy was 0.51 (95% CI, 0.09, 3.11) and was nonsignificant (Fig. 2). Other subanalyses were performed for BM thinning for two studies with OR of 0.90 (95% CI, 0.31, 2.68)[52,53] and BM thickness for two studies with OR of 0.23 (95% CI, −1.12, 1.58).[36,41] When the two studies reporting squamous metaplasia in AR patients were assessed,[52,53] there was significant reduction in the OR for the development of squamous metaplasia in patients using INCSs with an OR of 0.37 (95% CI, 0.15, 0.91; Fig. 3). This finding was not seen in CRS patients (OR, 1.14 [95% CI, 0.29, 4.55]).[45,46]

Risk of Bias

Comprehensive reporting of study methodology was inconsistent among RCTs and cohort studies (Tables 7 and 8). Among RCTs, sequence generation for randomization was invariably not reported. Nine studies (64%) blinded participants effectively. Only one study reported efforts to conceal allocation. Six RCTs (43%) addressed incomplete outcome data such as dropouts, and five RCTs (36%) were completely free of selective outcome reporting. Four RCTs (26%) excluded patients that had undergone prior nasal surgery, and nine

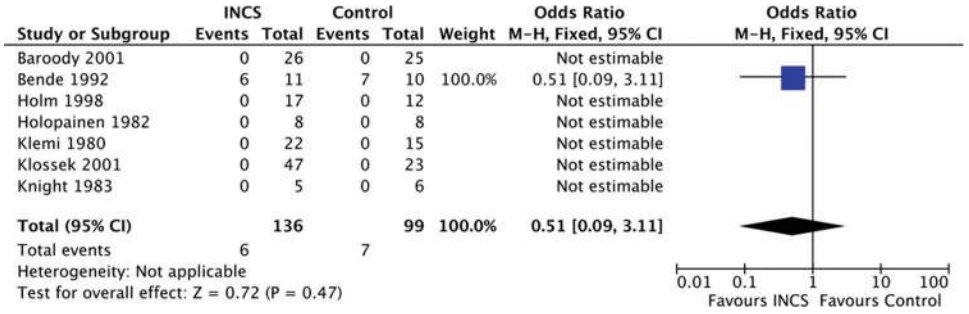

Figure 2. Forest plot of controlled studies measuring nasal mucosal atrophy as a defined outcome. An odds ratio (OR) less than one suggests a reduction in risk of mucosal atrophy and an OR that includes the value one implies similar risk between control and intranasal corticosteroids (INCSs).

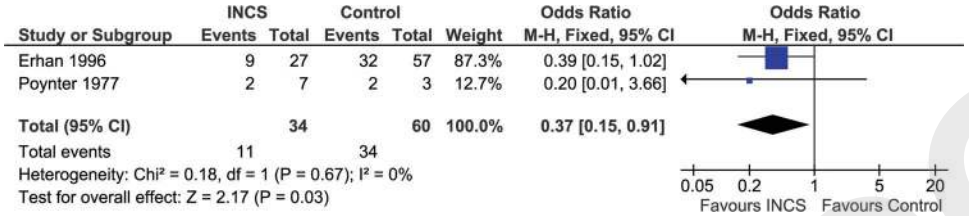

Figure 3. Forest plot of controlled allergic rhinitis (AR) studies measuring squamous metaplasia. An odds ratio (OR) less than one suggests a reduction in risk of squamous metaplasia and an OR that includes the value one implies similar risk between control and intranasal corticosteroids (INCSs).

RCTs excluded patients taking systemic corticosteroids. Eleven RCTs (79%) reported blinded histological assessments. Nine RCTs declared the involvement of pharmaceutical companies as authors or sponsors, with the remaining studies not publishing a conflict of interest statement.

In the non-RCT studies, eight studies (42%) excluded patients taking systemic corticosteroids, and only one study (5%) reported exclusion of patients with prior nasal surgery. Blinded histological assessment was performed in 13 studies (68%). Twelve studies (63%) reported adequate follow-up or accounted for incomplete outcome data. Ten studies (53%) declared involvement with a pharmaceutical company, either as authors or sponsors, with eight studies not including a conflict of interest statement. Only one study with a conflict of interest statement declared no financial interests among the authors.[40]

DISCUSSION

Systematic review of the literature indicated that mucosal atrophy is very uncommon in any group (control or intervention group). This finding held for studies involving patients with AR and NAR, and CRS with and without nasal polyps. Moreover, it was independent of the type, dose, or duration of INCS used. This lack of evidence for nasal atrophy is consistent with other reviews that have reported excellent safety and tolerability of INCSs.[8,21,54] Corticosteroids had no effect on the integrity of nasal epithelium or basement membrane and did not result in epithelial or basement membrane thinning, an increase in fibrosis or mucosal edema. When a meta-analysis was performed for the two studies that defined squamous metaplasia among patients with AR, a protective effect was observed.

The lack of evidence for atrophy of the respiratory nasal mucosa is not surprising. The role of skin as a physical and immunologic barrier has necessitated a keratinized stratified squamous epithelium and an extracellular matrix rich in lipid, collagen, and elastin.[55] Conversely, with the exception of small areas of vestibular squamous epithelium and olfactory neuroepithelium in humans, nasal mucosa comprises pseudostratified ciliated columnar epithelium with a superficial layer of mucus and is specialized for the warming, cleaning, and humidifying of air.[56,57] The mechanism of epidermal atrophy by topical glucocorticoids relies on the suppression of the mitotic rate of keratinocytes and fibroblasts,[58–60] thinning the lipid-rich stratum corneum of the epidermis, and decreasing the elasticity and tensile strength of the dermis. Moreover, glucocorticoids reduce extracellular matrix components, particularly type III collagen, lipid, and proteoglycans, further destroying the skin's barrier function.[61–63] The nasal mucosa has only a surface ciliated epithelium without a lipid-rich keratinized layer, a basement membrane, and an underlying lamina propria consisting of a loose connective tissue,[56] containing glands, blood vessels, and extravascular cells without the high density of elastin, collagen, and lipid found in skin. Such marked differences in structure and function between skin and nasal mucosa may make direct comparisons of pharmacodynamics and pharmacokinetics inappropriate.[4,55,56,64]

A number of CRS studies examined polyp biopsy specimens, in contrast to rhinitis studies where turbinate mucosa was sampled. The validity of extrapolating polyp biopsy studies to the population without nasal polyps is questionable because such findings may not represent histological changes in the remaining nasal mucosa, because marked differences in structure are well known between these tissues.[56,65]

No publications regarding nasal septal perforation met our inclusion criteria, despite the inclusion of this adverse effect in our search strategy. A number of case reports regarding nasal septal perforations in users of INCSs[12–15,66] were noted, and septal perforation is cited as an adverse effect in two case series.[18,20] These studies offer no histological assessment (thus excluded from this study) or control group and did not remove additional confounding factors associated with septal perforation including decongestant use, chemical insult, surgery or radiotherapy to the nose and sinuses, nose picking, and cocaine use.[67] These findings were not replicated by studies that examined histological changes to the nasal mucosa in patients using INCSs and likely represent very rare adverse effects. Taken together, there is insufficient evidence that INCSs represent a significant direct cause of nasal septal perforation.

The presence of tissue remodeling may affect the interpretation of studies in this review, especially in the absence of adequate controls. Tissue remodeling is a well-established concept in asthma and includes structural changes associated with thickening of the basement membrane, breaks in epithelial integrity, squamous metaplasia, and increased goblet cells and submucous glands.[68] Epithelial remodeling is seen in CRS, *viz.*, basement membrane thickening, epithelial shedding, and squamous metaplasia,[69–71] and is thought to be part of a natural nasal defense mechanism.[7] The loss of goblet cells and a change in submucous glands after treatment with INCSs in two CRS case series and one AR case series comparing baseline and posttreatment biopsy specimens[38,44,72] in this review may represent a partial slowing or reversal of the process of remodeling in the nasal airway, rather than atrophy. Importantly, the protective effect of INCSs for the development on squamous metaplasia in AR may prevent deleterious remodeling events.[73]

Table 7 **Cochrane Risk of Bias Assessment tool for RCTs**

Study	Population	Adequate Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Free of Selective Outcome Reporting	Free of Other Sources of Bias
Uller *et al.*[75] 2010	AR	Unclear	Unclear	Yes	Unclear	No	No
Baroody *et al.*[41] 2001	AR	Unclear	Unclear	Yes	Yes	Yes	No
Klossek *et al.*[36] 2001	AR	Unclear	No	No	Yes	Unclear	No
Holm *et al.*[51] 1998	AR	Unclear	Unclear	Unclear	Yes	Unclear	No
Braat *et al.*[76] 1995	AR	Unclear	Unclear	Yes	No	No	No
Knight *et al.*[43] 1983 (A)	Mixed rhinitis	Unclear	Unclear	Yes	Yes	Yes	No
Chang *et al.*[83] 2011	Mixed CRS	Unclear	Yes	Yes	Yes	Yes	No
Molet *et al.*[84] 2003	CRScNP	No	Unclear	Yes	Unclear	Yes	No
Saunders *et al.*[85] 1999	Nasal polyposis	Unclear	Unclear	Yes	Unclear	Yes	Unclear
Holopainen, Grahne *et al.*[45] 1982	Nasal polyposis	Unclear	Unclear	Yes	No	Unclear	No
Klemi *et al.*[46] 1980	Post-ethmoidectomy	Unclear	Unclear	Yes	Unclear	No	No

AR = allergic rhinitis; RCT = randomized controlled trial; CRS = chronic rhinosinusitis; CRScNP = chronic rhinosinusitis with nasal polyp.

Table 8 **Newcastle–Ottawa scale for assessment of risk of bias in cohort studies**

Study	Population	Representativeness of the Exposed Cohort	Selection of Nonexposed Cohort	Ascertainment of Exposure	Outcome Not Present at Baseline	Comparability of cohorts		Assessment of Outcome	Follow-Up >2 wk	Adequacy of Follow-Up
						Systemic Steroids	Prior Surgery			
Erhan *et al.*[52] 1996	NAR	*	*	*	*	#	#	#	*	*
Spector *et al.*[77] 1980	AR	#	*	*	*	*	#	*	*	*
Poynter *et al.*[53] 1977 (A)	AR	#	#	#	*	#	#	#	*	#
Alatas *et al.*[47] 2006	Nasal polyposis	#	#	*	#	#	#	*	*	*
Bende *et al.*[50] 1992	Mixed nasal polyposis/ AR	#	*	#	#	#	#	*	*	*

**Study met criteria.*
#Study did not meet criteria.
NAR = nonallergic rhinitis; AR = allergic rhinitis.

The limitations of this review include the wide heterogeneity of included studies with respect to definitions of atrophy and, consequently, the selection and measurement of outcomes. Only 17 studies specifically mentioned atrophy in the body of the article, despite including relevant histological outcomes. This represents the lack of a specific definition of mucosal atrophy. For example, it should be noted that the only controlled study to report a positive histological finding of mucosal atrophy[50] used "squamous metaplasia" to define atrophy (Fig. 2). Methods to assess epithelial thickness may have a high risk of bias because of the difficulty standardizing between biopsy samples and angles of histological sections. Studies such as Minshall *et al.*,[40] Baroody *et al.*,[41] and Fokkens *et al.*[30] that used an average of multiple measurements or quantification of length to cross-sectional area, may provide more robust assessments. Only selected English language publications were analyzed so Caucasian populations may be overrepresented. This review does not make any claims relating histological appearances to quality-of-life assessments and/or other patient-related outcomes. Despite newer treatment options such as specific immunotherapy, long-term use of INCSs will continue to be part of common rhinitis management and the questions addressed in the this review will continue to reflect patient and clinician concerns.[88]

CONCLUSIONS

There is no evidence in the existing literature to support a role of INCSs in the development of atrophy of the sinonasal mucosa. INCSs were not associated with nasal atrophy in patients with AR, NAR, and CRS with or without nasal polyps. Unlike skin, respiratory epithelium should not undergo corticosteroid-induced atrophy because of its simple pseudostratified structure. INCSs have a protective effect against squamous metaplasia in AR.

APPENDIX

Electronic Search Strategy

Population.
Patients using INCSs.
Intervention.
Intra-nasal steroids
Comparison.
N/A
Outcome.
Atrophy of the nasal Mucosa.
Time Period.
Search Strategy.
Disease/Population results AND intervention results AND outcome =

Population: sinusitis or rhinitis or sinusiti* or rhinosinusiti* or nasosinusiti* or pansinusiti* or ethmoiditi* or antriti* or sphenoiditi* or paranasal sinus diseases/ not neoplasm or (sinus* or sinonasal or endonasal or paranasal or nose or nasal or rhinosinus*) adj3 (inflammation or inflamed or pain* or infect* or purulen* or obstruct* or block* or drainage or discharg* or symptom* or disease*) or nasal polyps.

Intervention: (steroid or corticosteroid or glucocorticoid or corticoid or (anti-inflammatory agents not anti-inflammatory agents, nonsteroidal) or beclamet* or beclocort* or beclometasone or becotide) or (betamethason* or betametasone or betadexamethasone) or (hydrocortison* or cortiso* or celesto) or (dexamethason* or dexamethasone or hexadecardrol or decadron or dexasone or hexadrol) or (budesonid* or horacort or pulmicort or rhinocort or methylfluorprednisolone) or (flunisolid* or nasalide or millicorten or oradexon) or (fluticason* or flonase or flounce or mometason* or nasonex) or (triamcinolon* or nasacort or tri next nasal or aristocort or volon)) and (nasal or intranasal or topical or nose or spray or sinus or sinonasal* or endonasal* or paranasal* or aerosol*).

Outcome: atrophy or (wast* or atrophy or atroph* or thinning* or thin*) or ((nasal or intranasal or nose or sinus or sinonasal or endonasal or paranasal) and (biops* or histol* or histopath* or patholo* or microscop*)) or (nasal and (septum or septal) and perforat*) or ulcer or ulcerat.*

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