



Mucosal remodeling and reversibility in chronic rhinosinusitis

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Purpose of review

Evidence suggests that some structural changes caused by mucosal remodeling may be primarily irreversible, which theoretically challenges the current management model of chronic rhinosinusitis (CRS). The relationship between inflammation and remodeling in the mucosa remains complex, yet better understanding of involved pathways holds potential clinical implications. This article reviews the controversies as well as current applications from the literature.

Recent findings

First, the relationship between inflammation and remodeling is a complex one involving multiple pathways, with evidence suggesting that remodeling is not a simple fibrotic end-stage process secondary to long-standing inflammation. Second, anti-inflammatory approaches alone are probably not successful in reversing changes such as collagen deposition, indicating that early treatment might be crucial for preventing disease progression. Third, a dysfunctional sinus remains a pure clinical/surgical phenomenon with lack of histological characterization. Fourth, maximal/extensive surgical techniques are advocated for patients with severe disease or dysfunctional sinuses.

Summary

Reversibility of remodeling holds implications for the management of CRS. Although clinical applications (both medical and surgical) exist, further research is required for solidifying current evidence as well as exploring new avenues for therapy.

Keywords

chronic rhinosinusitis, dysfunctional sinus, endoscopic sinus surgery, irreversible mucosal disease, mucosal remodeling

INTRODUCTION

Remodeling is an important process that occurs throughout the body and is involved in normal tissue healing and repair in a physiological state. Remodeling consists of a cycle of deposition and removal of extracellular matrix (ECM) proteins. However, this delicate balance can be altered, and this has been implicated in disease states such as asthma.

Asthma was traditionally considered a simple reversible narrowing of the lower airways, but new research suggests that damage occurs with potential irreversible effects, both clinically and histologically. The role of remodeling has been a dynamic area of research in asthma, which has suggested a correlation between remodeling, severity of the disease and irreversible decline in pulmonary function. This enhanced understanding resulted in modifications in steroid use in asthma [1].

Strong links exist between upper and lower airway disease, amounting to the description of a

‘unified airway’ [2]. Similar remodeling processes in both asthma and chronic rhinosinusitis (CRS) have been described [3]. However, the question arises as to whether the same irreversible changes observed in asthma are also present in CRS. Reversibility – or lack thereof – of histological changes occurring in CRS could have significant clinical implications similar to asthma, but to date, these potential implications have been sparsely addressed in the CRS literature. Investigating the potential for mucosal reversibility is of particular importance in CRS, as current treatment paradigms hinge on

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KEY POINTS

- Remodeling in the sinuses can lead to potential irreversible structural changes and thus poses a theoretical threat to the current management model of CRS.
- The relationship between inflammation and remodeling is a complex one involving multiple pathways, with the evidence suggesting that remodeling is not a simple fibrotic end-stage process secondary to long-standing inflammation.
- A dysfunctional sinus remains a pure clinical/surgical phenomenon with lack of histological characterization.
- Anti-inflammatory approaches alone are probably not successful in reversing changes such as collagen deposition, indicating that early treatment might be crucial for preventing disease progression.
- Maximal/extensive surgical techniques are advocated for patients with severe disease or dysfunctional sinuses.

functional endoscopic sinus surgery (FESS) and topical intranasal steroids with the expectation that remodeled diseased mucosa can revert to a physiologic state. The success of FESS portrays an image of CRS with reversible potential when treated with medication to abort the inflammatory mechanisms and surgery to improve delivery of those medications. Remodeling thus poses a theoretical threat

to this management model (or at minimum, our understanding of it), if structural changes are primarily irreversible (Fig. 1).

A brief overview of the structural features of remodeling that occurs in the sinuses is provided in Table 1. The exact details of these features are not the subject of this review and are discussed elsewhere. The aim of this article is to review the potential clinical implications of remodeling in the sinuses, which revolve around the probable (or improbable) reversibility of these structural modifications with various therapies.

REMODELING AND INFLAMMATION

To discuss the subject of reversibility in remodeled mucosa, the complex relationship between remodeling and inflammation warrants review.

Remodeling: end-stage phenomenon or active primary process?

Traditionally, remodeling is viewed as a secondary process that occurs due to a longstanding inflammatory process, which culminates in increased ECM deposition, basement membrane thickening, and irreversibly remodeled mucosa. This theory of irreversible mucosal changes in the airway has been recently challenged, primarily in the asthma literature, where it has been suggested that remodeling is an active primary process that is at least partially independent of inflammation, perhaps

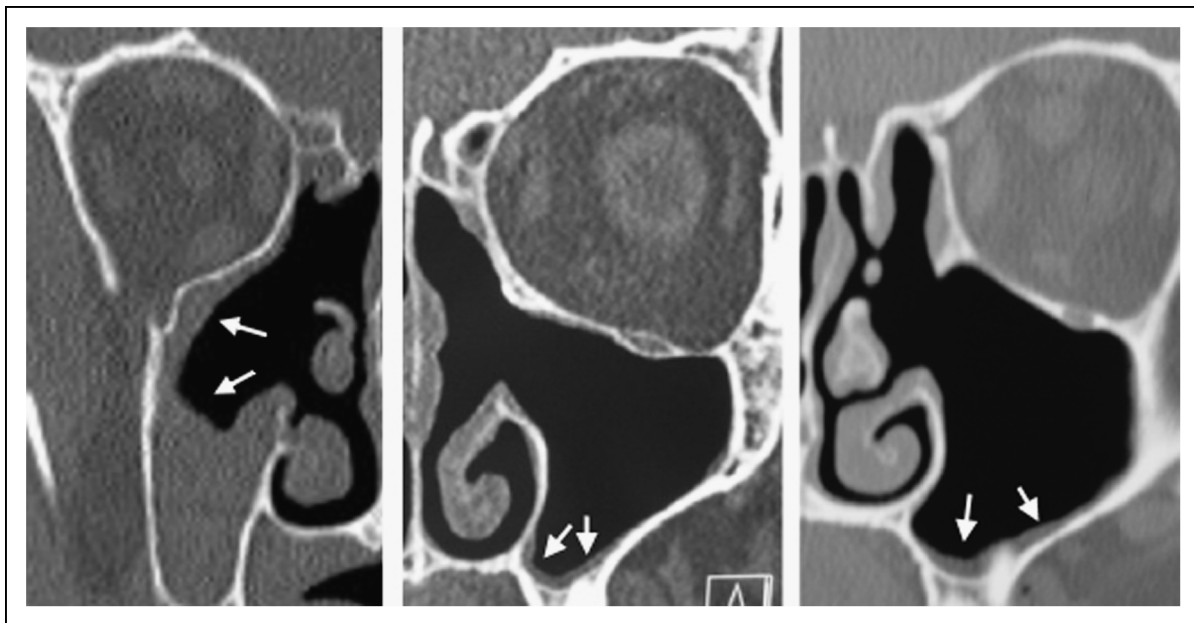


FIGURE 1. Computed tomography scans of three different patients with previous functional endoscopic sinus surgery demonstrating diseased/thickened mucosa in the maxillary sinuses (white arrows) despite presumably adequate sinus ventilation.

Table 1. A brief overview of the characteristic mucosal changes of remodeling in the sinuses

Site	Feature
Epithelium	Epithelial damage and erosions
	Goblet cell hypertrophy and mucus hypersecretion
Mucosa	Subepithelial basement membrane thickening and collagen deposition
	Myofibroblast accumulation with subsequent deposition of ECM molecules
	Pseudocyst formation in nasal polyps
Bone	Bone erosion and/or thickening

ECM, extracellular matrix.

even commencing in parallel with the inflammatory process [4].

One argument against the theory that remodeling is primarily the end-stage fibrosis resulting from an inflammatory process stems from study of the ultrastructure of the thickened subepithelial basement membrane as well as the timing of its formation. Basement membrane thickening is primarily the result of collagen deposition, which is a hallmark of the remodeling process in both upper and lower airways. In asthmatic bronchi, this thickening is due to deposition of reticulin fibers, mainly composed of collagen types III and V, which contrasts the prominence of type I fibrils in fibrosis and scar formation [5]. The predominance of type III and V collagen has also been reported in mucosal remodeling in CRS [6]. Another argument against remodeling being the end-product of inflammation is that the remodeling process is seen starting at an early age, with readily demonstrable thickened reticular basement membrane (RBM) in children with both mild and severe asthma [7–9]. It can be postulated that the effects of inflammation require more time to form such prominent RBM thickening. Further evidence suggesting against a temporal relationship between inflammation and remodeling in asthma was reported by Boulet *et al.* [10], who found that type I and type III collagen deposition beneath the basement membrane was similar in recently diagnosed and long-standing asthmatic patients, whereas Payne *et al.* [11] found that RBM thickness in children with asthma was not statistically different from that seen in adult asthmatic patients.

In contrast, review of the CRS literature supports the temporal aspect of remodeling. For instance, Rehl *et al.* [12] compared basement membrane thickness between control and CRS specimens. They found that diseased patients had thicker basement membranes. In addition, the thickness correlated positively with the duration of disease among

diseased patients. Other studies [13–15] similarly found that features of remodeling such as basement membrane thickening and goblet cell hyperplasia were more prominent in adult CRS when compared with pediatric or adolescent CRS, lending further evidence for the temporal relationship that starts with inflammation and results in tissue remodeling.

Remodeling and eosinophilic inflammation: a direct correlation?

Although existing evidence suggests that remodeling does not occur as a direct result of inflammation, it is still highly plausible that the two processes are strongly related. The primary regulator of the remodeling process is transforming growth factor beta (TGF-β), which induces fibroblast proliferation as well as differentiation of fibroblasts into myofibroblasts. These cells are responsible for deposition of collagen and other ECM components. The key source of TGF-β is inflammatory cells, most notably eosinophils [16,17], which are the main effector cells in asthma and CRS. The central role of eosinophils in remodeling has been further elucidated in studies of both interleukin 5 (IL-5)-deficient mice [18,19] and eosinophil-deficient mice [20]. IL-5 is expressed by T cells, as well as eosinophils, and is important in eosinophil proliferation. These mice, unable to mount a proper eosinophilic response, were found to be protected from increased peribronchiolar collagen deposition and airway smooth muscle when compared with sham control mice [18,20].

Basement membrane thickness has also been reported to correlate with the density of underlying eosinophils both in sinusitis [21] and asthma [22]. It is particularly interesting that features of mucosal remodeling in the sinuses have consistently been reported to be more prominent in those with comorbid asthma [12,23,24]. As CRS patients with asthma have higher eosinophilic load [23–26], it is inferred that remodeled mucosa is due to increased eosinophils and thus myofibroblasts and levels of TGF-β. This corresponds clinically, as asthmatic CRS patients have significantly increased TGF-β and myofibroblasts in sinus mucosa when compared with nonasthmatic individuals [26]. Further evidence for a relationship between remodeling and inflammation is present in the distribution of TGF-β and myofibroblasts, which coincides with the increased concentration of eosinophils in the nasal polyp pedicle [27,28]. Eosinophils also produce IL-11 and IL-17, both having profibrotic effects [6,21] and positive correlation with epithelial damage and collagen deposition in the basement membrane [4,19].

Another proposed role of eosinophilic inflammation in the remodeling process is through alteration of balance between the matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). MMPs are involved in hydrolyzing components of the ECM and play a central role in tissue remodeling, whereas TIMPs inhibit metalloproteinase activity resulting in decreased ECM turnover. Therefore, a tipped MMP–TIMP balance results in accumulation of ECM proteins, which is seen clinically in formation of nasal polyps, especially when massive polyposis with aggressive recurrence are present. In fact, recurrence correlates positively with the eosinophilic load in the polyps [29,30[¶]]. Specifically, MMP-9 is thought to play an integral role (with TIMP-1) in tissue remodeling and has been positively associated with eosinophils [31–33]. MMP-9-positive cells were detected in increased numbers in pseudocyst formations in polyps [34], thus implicating MMP-9 in polyp core edema, with subsequent increased polyp size and potential accelerated polyp recurrence. This can be demonstrated in the aspirin-sensitive subgroup, which histologically exhibits higher grade mucosal eosinophilia than the aspirin-tolerant subgroup [25], and clinically presents with larger polyps, higher Lund–Mackay scores [35–37] and more aggressive recurrence [38[¶],39,40]. In this subgroup, the MMP-9:TIMP-1 ratio was found to be elevated (when compared with the aspirin-tolerant subgroup) [41[¶]], further supporting a role for MMPs and TIMPs in polyp growth and recurrence.

Another mechanism through which eosinophils can affect the remodeling process is through cysteinyl leukotrienes (CysLTs) [20,42,43]. The consistent overproduction of CysLTs (and their receptors) in the presence of aspirin sensitivity [44,45] could be an additional explanatory factor for the thicker subepithelial basement membrane found in this group [12]. The role of CysLTs in remodeling has been demonstrated in mouse asthma models, wherein CysLT-1 receptor blockage caused suppression of the development of remodeling in the mucosa [43,46,47]. As mentioned previously, the prominence of CysLTs in the aspirin-sensitive population secondary to deranged eicosanoid metabolism, coupled with the diffuse polyposis and high recurrence rates occurring in these patients, suggests an implication of CysLTs in the mucosal remodeling process.

Eosinophilia and remodeling: conflicting evidence?

Despite the previous studies, the contribution of eosinophilic inflammation to the remodeling

process is not straightforward. Baraldo *et al.* [48] compared eosinophilic with noneosinophilic asthmatic children and reported that remodeling occurred to a similar degree in both groups. This finding suggests that remodeling can occur even in the absence of prominent eosinophilia, thus indicating the involvement of other mechanisms [48]. Further evidence for a remodeling pathway that does not rely as heavily on eosinophils is found in CRS. Tissue obtained from patients suffering from CRS with nasal polyps (CRSwNP) has been reported to have less collagen deposition and TGF- β despite higher loads of mucosal eosinophilia than CRS without polyps (CRSsNP) [49,50]. Remodeling also occurred consistently in nasal polyps of both western and Asian populations [50,51[¶]], despite different inflammatory profiles and generally lower levels of eosinophils in Asian sinusitis [52–54].

In summary, remodeling may not be a simple end-stage consequence of long-standing inflammation. However, parallel processes may occur with ongoing inflammation continuously contributing to remodeling. In tandem, remodeling can also contribute to inflammation, as fibroblasts release eosinophil chemoattractants such as eotaxins and regulated upon activation, normal T-cell expressed, and secreted (RANTES, also known as CCL-5) [55,56]. Although the effector cells and inflammatory pathways may differ, the role of cytokines in remodeling remains intriguing, and how this ultimately results in the similar clinical symptoms of sinusitis, irrespective of the underlying inflammatory profile.

MEDICAL THERAPY AND REMODELING

Steroids are the mainstay of treatment in inflammatory airway disease, so it is important to investigate their effects on remodeling. Steroids have the theoretical potential to reverse remodeling through two primary means. The first is the ability to reverse pathologically remodeled airways by decreasing collagen deposition in the subepithelial basement membrane. The second possibility is that steroids delay or modify the remodeling process through anti-inflammatory actions. The former action has been frequently researched, mainly via assessment of collagen deposition. A number of these studies [10,57–59] (including two on sinus disease [6,60]) conclude that steroids do not effectively reverse collagen deposition (Table 2) [6,10,57–64]. This topic is not without debate, however, and other studies argue in favor of reversibility [61–64] (Table 2), though some suggest that reversibility may be attributable to high steroid dosage and long treatment duration [61]. Although the latter

Table 2. Effect of corticosteroids on collagen deposition in the reticular basement membrane

Study	Airway	Steroid	Observation	Conclusion
Boulet <i>et al.</i> [10]	Lower airway	Metered-dose inhaler of FP 250 µg per inhalation, and asked to take two inhalations twice a day for 8 weeks	Baseline type 1 and type 3 collagen deposition underneath the BM was similar in recently developed asthma and long-standing asthma and did not change significantly after FP	Irreversible
Chakir <i>et al.</i> [57]	Lower airway	2-week oral methylprednisolone 40 mg/day	Treatment with corticosteroids did not decrease the expression of types I and III collagens	Irreversible
Baraket <i>et al.</i> [58]	Lower airway	Low dose (100 µg twice daily) versus high dose (500 µg twice daily) inhaled FP	No change in BM thickness in the group as a whole and no differences between low-dose and high-dose FP	Irreversible
Chakir <i>et al.</i> [59]	Lower airway	ICS dose adjusted to maintain asthma control for 1 month. This minimum ICS treatment was then continued for 24 months	No change in collagen deposition underneath the BM was observed	Irreversible
Ward <i>et al.</i> [61]	Lower airway	FP 750 µg FP twice daily for 3 and 12 months	RBM thickness decreased in the FP group, but only after 12 months of treatment	Reversible
Olivieri <i>et al.</i> [62]	Lower airway	FP (250 µg twice daily) or matched placebo for 6 weeks	BM thickness was significantly decreased when compared with that of the placebo group	Reversible
Trigg <i>et al.</i> [63]	Lower airway	BDP, 500 µg twice per day or placebo was administered for 4 months	Thickness of type III collagen deposition in the bronchial lamina reticularis reduced	Reversible
Hoshino <i>et al.</i> [64]	Lower airway	Inhaled BDP, 400 µg twice a day or placebo, for 6 months	Significant decrease in the thickness of the lamina reticularis	Reversible
Molet <i>et al.</i> [6]	Upper airway	Two 50 µg intranasal sprays of FP per nostril twice daily versus matching placebo-containing diluents, for 4 weeks	No significant effect on deposition of any collagen type	Irreversible
Mastruzzo <i>et al.</i> [60]	Upper airway	100 µg of budesonide in each nostril twice daily, for 8 weeks	No observable differences in collagen staining or distribution before and after treatment	Irreversible

BDP, beclomethasone dipropionate; BM, basement membrane; FP, fluticasone dipropionate; RBM, reticular basement membrane.

(anti-inflammatory) action of steroids is well established, its impact on altering the course of remodeling and the specific clinical benefit of early intervention in this case have not been fully elucidated in CRS.

Exploiting different pathways, other medications have also been investigated in targeting remodeling. One such medication, mepolizumab (IL-5 antagonist), was administered via intravenous infusions to mild atopic asthmatic patients on β_2 -agonist therapy [65]. The researchers found that the treated patients had reduced ECM protein deposition in the basement membrane in addition to decreased airway eosinophil numbers with lower TGF- β 1 mRNA expression and lower concentration of TGF- β 1 in bronchoalveolar lavage fluid [65]. Another medication, montelukast, is a leukotriene antagonist that demonstrated in mouse asthma models that CysLT receptor blockade is capable of suppressing features of remodeling [43,46,47].

In addition, through targeting MMPs, doxycycline has been found in one study [65] to function comparably to oral steroids in decreasing nasal polyp size. Doxycycline's action is thought to occur through an inhibitory effect on MMP-9, eosinophil cationic protein (ECP), and myeloperoxidase [66]. Future research is needed to further delineate the role of medications in inhibiting remodeling and inflammation.

SURGERY AND REMODELING

Endoscopic surgery has become the standard practice for patients with CRSwNP and CRSsNP who remain symptomatic despite maximal medical therapy. The great clinical success achieved with FESS contributes to the belief that majority of pathologically remodeled mucosa is reversible to a more physiologic state. Improvement is seen grossly in sinuses postoperatively with decreased polyp

burden, edema, and erythema; yet, less has been studied at a tissue level. In fact, contrary to surgical results, the limited available histological studies [67,68] suggest that despite clinical improvement, electron microscopy continues to demonstrate irreversible mucosal changes after surgery. Clinically, this failure of mucosa to revert to a normal state may be only evident in a small subset of patients who suffer from what some authors describe as a dysfunctional sinus or clinically irreversible sinus disease [69–72].

A dysfunctional sinus is the one that has apparently lost its mucociliary function despite maximal medical treatment and surgery achieving adequate sinus ventilation (Fig. 2). This clinical situation may be related to irreversible changes in the mucosa secondary to a pathologic remodeling process [73]. It is plausible that a majority of disease states are capable of reverting. In these states, standard FESS is sufficient to restore a physiologic state, whereas on the other end of spectrum are the severely diseased states that require more significant measures to restore function (or at least clinical improvement).

Although mucosal remodeling in the sinuses can lead to potentially irreversible changes in the mucosa and basement membrane, no studies to date have shown clear links between remodeling and dysfunctional sinuses. As a result, a dysfunctional sinus remains a pure clinical/surgical phenomenon with lack of histological characterization. Despite the paucity of research describing a direct link, clinical evidence supports a surgical philosophy that a radical/extended surgical approach (rather than conservatively targeting osteomeatal complex

obstruction) may lead to improvement – even in patients deemed to have clinically irreversible disease. As a result, maximal surgical techniques for dysfunctional sinuses are advocated [74]. Over the years, the face of these surgeries has changed, but the concept remains the same – remove the severely diseased tissue to reverse pathologic mucosal remodeling. Examples of these operations include: the Caldwell–Luc (with mucosal stripping) [71,75] and canine fossa trephine (with preservation of a thin layer of mucosa) [76,77] for a dysfunctional maxillary sinus and the Draf-III frontal drillout (modified Lothrop) procedure [78,79] for dysfunctional frontal sinuses. These surgeries (other than the traditional Caldwell–Luc) theoretically remove the pathologic inflammatory cells with their associated cytokines and chemokines, thus decreasing the inflammatory load and providing a milieu conducive to normal mucosal regeneration. This regeneration has been suggested to occur with no permanent sinus damage if the periosteum was left intact [72]. Considering the close links between inflammation and remodeling, we hypothesize that the benefit of these radical procedures is most prominent in patients with refractory disease and the highest inflammatory burdens (such as these with comorbid asthma or aspirin intolerance) [75,80,81].

The ability of sinus mucosa to reverse pathologic changes could be a factor in determining the quality of recovery after surgery. Targeted therapy to prevent remodeling, therefore, has potential to improve postoperative outcomes. For example, poor healing after surgery has been linked to elevated levels of MMP-9 in nasal secretions preoperatively

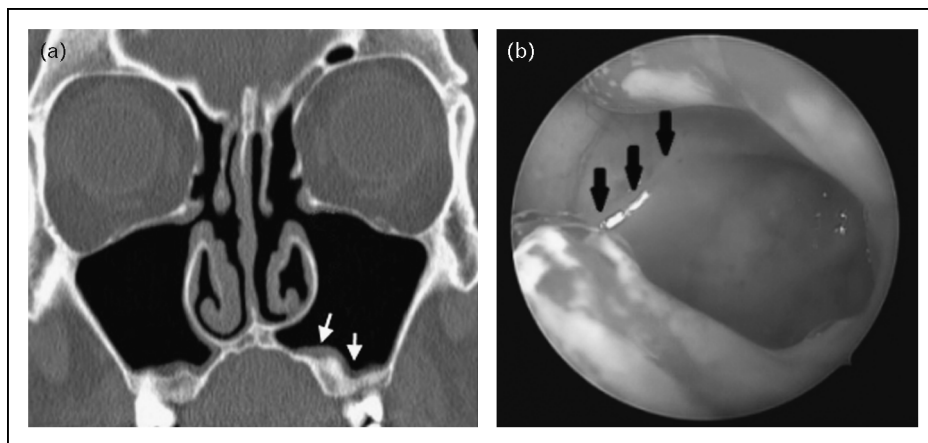


FIGURE 2. Mucus stasis inside a maxillary sinus: a dysfunctional sinus is a poorly defined clinical phenomenon with no histological characterization. The computed tomography scan (a) gives an impression of an adequate antrostomy with minimal disease in the maxillary sinuses; however, thickened/diseased mucosa is still evident (white arrows) and the endoscopic picture (b) of the same sinus shows mucus stasis.

and postoperatively [82,83]. As inflammatory cells are the major source of MMP-9, residual leukocytes left in the sinuses during sinus surgery could be causative of poor mucosal recovery after surgery through the production of elevated levels of MMP-9. This supports the theory that surgery should aim at reducing the pathologic tissue and thus inflammatory load [84[¶]]. In line with this thought process, Huvenne *et al.* [85] studied the effects of doxycycline as an anti-MMP-9 therapy in the form of doxycycline-bearing stents in post-operative patients. In this pilot study [85], improved healing quality was suggested based on endoscopic evaluation. Similarly, evidence suggests that chitosan gel improves wound healing and reduces adhesions after sinus surgery [86,87]. One explanation for the benefits of chitosan is that chitin derivatives like chitosan inhibit MMP-2 and MMP-9 [88,89]. Adjunct therapies to surgery could thus have positive effects to encourage reversal of pathologically remodeled mucosa and should remain an active area for research.

CONCLUSION

The relationship between inflammation and remodeling in CRS is a complex one and not yet completely understood. Recent evidence suggests mucosal remodeling is an active and complex process that is not necessarily an unavoidable fibrotic consequence of continued inflammation. In CRS, as well as asthma, the relationship between inflammation and remodeling is a complex one involving a multitude of overlapping pathways. The wide array of cellular and cytokine players include neutrophils, eosinophils, various interleukins, TGF- β , MMPs, TIMPs, and CysLTs, just to name a few. Interestingly, similar structural changes have been demonstrated regardless of the prevailing underlying inflammatory profile [51[¶]]. The complexity of the inflammatory profiles in all likelihood reflects the underlying heterogeneity of the different 'endotypes' of inflammatory airway disease [90–92].

With the strong link between inflammation and remodeling, anti-inflammatory medications (topical steroids being the gold standard) have the potential to delay the onset of remodeling and alter the course of the disease. However, studies suggest that anti-inflammatory approaches alone are not successful in reversing changes such as collagen deposition, indicating that early treatment might be crucial for preventing disease progression. Novel antieosinophilic treatments such as IL-5 antagonists and leukotriene antagonists may exhibit additional benefit in controlling the disease, especially in

patients with high eosinophilic loads. Anti-MMP therapy also possesses the potential to modify healing quality after surgery and influence matrix deposition, which may prove important in tempering polyp growth and recurrence. Future studies are needed to discern the efficacy and indications for these medical interventions.

Surgery is a treatment option applicable to the sinonasal passages, which is not available to address diseased bronchial mucosa, and surgery has demonstrated benefit in those who fail medical therapy for CRS. Due to remodeled mucosa, the conservative philosophy of FESS and minimally invasive sinus technique to relieve ostial obstruction is very likely insufficient in handling severe disease states with high inflammatory loads and/or a dysfunctional mucosa (Fig. 1). These patients derive more benefit from maximal surgical options directed toward eliminating the inflammatory load and improving access for topical medication to retard or reverse the mucosal damage. Additionally, removal of irreversibly diseased mucosa allows healthy mucosa to regenerate in its place [72]. Due to the complexity of disease in recalcitrant sinusitis, it is likely that multimodality treatment will serve these patients best.

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Conflicts of interest

No funding was received for this study.

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P.-J.W. is a member of a consortium that has patented the use of chitosan gel in the sinuses after surgery.

No other conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 119).

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