Mucosal Remodeling and Reversibility in CRS


**Mucosal remodeling and reversibility in chronic rhinosinusitis.**

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**Presented by:**

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• **Remodeling:**
  • Important process occurs throughout the body and involved in normal tissue healing and repair in a physiological state.
  • Consists of a cycle of deposition and removal of extracellular matrix (ECM) proteins.
  • This delicate balance can be altered, and this has been implicated in disease states such as asthma.
• Asthma was considered a simple reversible narrowing of the lower airways.
• New research suggests that damage occurs with potential irreversible effects, both clinically and histologically.
• Research in asthma suggested a correlation between remodeling, severity of disease and irreversible decline in pulmonary function.
• Strong links exist between upper and lower airway disease, amounting to the description of a ‘unified airway’.
• Similar remodeling processes in both asthma and CRS have been described.
• Question arises as to whether the same irreversible changes observed in asthma are also present in CRS.
Investigating the potential for mucosal reversibility is of particular importance in CRS, as current treatment paradigms hinge on FESS and topical intranasal steroids with the expectation that remodeled diseased mucosa can revert to a physiologic state.
• 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 poses a theoretical threat to this management model, if structural changes are primarily irreversible.
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>
<thead>
<tr>
<th>Site</th>
<th>Feature</th>
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<tbody>
<tr>
<td>Epithelium</td>
<td>Epithelial damage and erosions</td>
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<td>Goblet cell hypertrophy and mucus hypersecretion</td>
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<td>Mucosa</td>
<td>Subepithelial basement membrane thickening and collagen deposition</td>
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<td>Myofibroblast accumulation with subsequent deposition of ECM molecules</td>
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<td></td>
<td>Pseudocyst formation in nasal polyps</td>
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<tr>
<td>Bone</td>
<td>Bone erosion and/or thickening</td>
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ECM, extracellular matrix.
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 even commencing in parallel with the inflammatory process.
• 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.

The predominance of type III and V collagen has also been reported in mucosal remodeling in CRS.
• 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.

• It can be postulated that the effects of inflammation require more time to form such prominent RBM thickening.
Further evidence found that type I and type III collagen deposition beneath the basement membrane was similar in recently diagnosed and long-standing asthmatic patients and also 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.
• one study compared basement membrane thickness between control and CRS specimens and found that diseased patients had thicker basement membranes and the thickness correlated positively with the duration of disease among diseased patients.
• Other studies 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

- 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-b), which induces fibroblast proliferation and differentiation of fibroblasts into myofibroblasts.
- These cells are responsible for deposition of collagen and other ECM components.
• Source of TGF-b is inflammatory cells (Eosinophils), which are the main effector cells in asthma and CRS.
• IL-5 is expressed by T cells, as well as eosinophils, and is important in eosinophil proliferation.
• Features of mucosal remodeling in the sinuses have consistently been reported to be more prominent in those with comorbid asthma.

• As CRS patients with asthma have higher eosinophilic load, remodeled mucosa is due to increased eosinophils and thus myofibroblasts and levels of TGF-b.
• Asthmatic CRS patients have significantly increased TGF-b and myofibroblasts in sinus mucosa when compared with nonasthmatic individuals.

• Further evidence for a relationship between remodeling and inflammation is present in the distribution of TGF-b and myofibroblasts, which coincides with the increased concentration of eosinophils in the nasal polyp pedicle.

• Eosinophils also produce IL-11 and IL-17, both having profibrotic effects and positive correlation with epithelial damage and collagen deposition in the basement membrane.
Eosinophilia and remodeling

- Despite the previous studies, the contribution of eosinophilic inflammation to the remodeling process is **not** straightforward.
- One study 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.
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).
• 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.
MEDICAL THERAPY AND REMODELING

- **Steroids** are the mainstay of treatment in inflammatory airway disease.
- Steroids have the theoretical potential to **reverse remodeling** through two primary means.
  - **First** is the ability to reverse pathologically remodeled airways by decreasing collagen deposition in the subepithelial basement membrane.
  - **Second** is that steroids delay or modify the remodeling process through anti-inflammatory actions.
- Steroids do not effectively reverse collagen deposition.
- This topic is not without debate, however, and other studies argue in favor of reversibility, though some suggest that reversibility may be attributable to high steroid dosage and long treatment duration.
- Although 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.
• Other medications have also been investigated in targeting remodeling.

• **Mepolizumab** (IL-5 antagonist), was administered via intravenous infusions to mild atopic asthmatic patients on b2-agonist therapy.

• Reduce ECM protein deposition in BM

• Decrease airway eosinophil numbers

• lower concentration of TGF-b1 in bronchoalveolar lavage fluid.
• **montelukast**, leukotriene antagonist that demonstrated in mouse asthma models that cysteinyi leukotrienes CysLT receptor blockade is capable of suppressing features of remodeling.

• **Doxycycline** found in one study to function comparably to oral steroids in decreasing nasal polyp size.
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.
available histological studies 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.
A dysfunctional sinus is the one that has apparently lost its mucociliary function despite maximal medical treatment and surgery achieving adequate sinus ventilation.

This clinical situation may be related to irreversible changes in the mucosa secondary to a pathologic remodeling process.

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.
**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.
• A dysfunctional sinus remains a pure clinical/surgical phenomenon with lack of histological characterization.

• Clinical evidence supports **Radical/extended surgical approach** may lead to improvement.

• As a result, **maximal surgical techniques** for dysfunctional sinuses are advocated.
Examples of these operations include:

- Caldwell–Luc (with mucosal stripping),
- Canine fossa trephine (with preservation of a thin layer of mucosa) for a dysfunctional maxillary sinus
- Draf-III frontal drillout (modified Lothrop) procedure for dysfunctional frontal sinuses.
SUMMARY

- Relationship between inflammation and remodeling is complex and involving multiple pathways.
- Evidence suggests that remodeling is not a simple fibrotic end-stage process secondary to longstanding inflammation.
- Anti-inflammatory approaches alone are probably not successful in reversing changes such as collagen deposition.
- Early treatment might be crucial for preventing disease progression.
- Dysfunctional sinus remains a pure clinical/surgical phenomenon with lack of histological characterization.
- Maximal/extensive surgical techniques are advocated for patients with severe disease or dysfunctional sinuses.
References

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