

## Review Article

# Sinonasal Tissue Remodelling during Chronic Rhinosinusitis

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The purpose of this review is to summarise contemporary knowledge of sinonasal tissue remodelling during chronic rhinosinusitis (CRS), a chronic disease involving long-term inflammation of the paranasal sinuses and nasal passage. The concept of tissue remodelling has significant clinical relevance because of its potential to cause irreversibility in chronic airway tissues. Recent studies have indicated that early surgical treatment of CRS may improve clinical outcome. Tissue remodelling has been described in the literature extensively with no consensus on how remodelling is defined. This review describes various factors implicated in establishing remodelling in sinonasal tissues with a special mention of asthma as a comorbid condition. Some of the main histological features of remodelling include basement membrane thickening and collagen modulation. This may be an avenue of research with regard to targeted therapy against remodelling in CRS.

## 1. Introduction

Epidemiological data suggest chronic rhinosinusitis (CRS) affects at least 5% of the general population [1]. Despite protocolised medical and surgical intervention from international consensus documents recurrence rates remain problematic [2]. The aetiology of the recurrent disease remains elusive. Recent data suggest early surgical intervention may reverse disease progression and prevent recurrence [3]. Research indicates that patients who receive surgery within 12 months of being diagnosed with CRS have a significant reduction in healthcare compared with those patients treated after more than five years of duration of disease [4].

The respiratory mucosa of the nasal passage is continuously exposed to the particles in the inhaled air. In health, the epithelium, cilia, and mucus function together to ensure efficient mucociliary clearance. Impaired mucociliary clearance in CRS likely represents one of the first pathogenic steps in the chronic nature of this disease [5]. The sinus ostia in patients with CRS are obstructed and altered microbiota profiles and mucosal inflammatory responses are observed

[5]. Tissue remodelling is a key element in the resultant histopathological changes of the mucosa.

Tissue remodelling comprises the cyclical deposition and degradation of extracellular matrix (ECM) [6, 7]. This dynamic process is an integral part of the tissue response to injury or inflammation in general. Tissue remodelling often leads to a restoration of normality; however, an aberration in this process results in progression to a pathological state [8] (Figure 1).

Traditionally, tissue remodelling is viewed as a secondary phenomenon, appearing late in the disease process consequent to persistent inflammation [9]. However, more recently tissue remodelling after an injury has been shown to occur in parallel to inflammation, rather than the two being consecutive phases of the response to injury [10–12]. These observations suggest remodelling may occur early in the disease process in CRS. Pathological endotyping or subphenotyping of remodelling features may potentially identify patients at higher risk of recurrent or persistent disease.

There is currently no consensus on how to define remodelling. The most common approach is to identify squamous metaplasia, subepithelial fibrosis, and basement

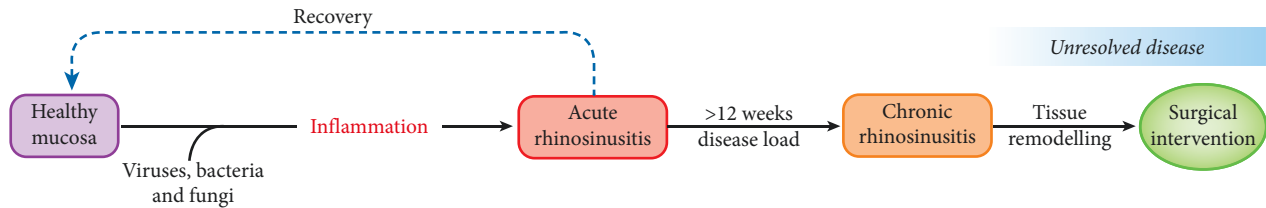


FIGURE 1: Progression of disease in chronic rhinosinusitis. Inflammation observed in acute rhinosinusitis caused by viruses, bacteria, and fungi can resolve to a healthy state or can proceed to CRS if the inflammation persists longer than 12 weeks. The chronic nature of disease induces widespread tissue remodelling of the paranasal sinuses and nasal passage. Unresolved CRS often requires surgical intervention to remove purulent, stagnant mucous, and inflamed tissue.

membrane thickening [13]. This implies tissue remodelling in the sinonasal mucosa involves both the epithelium and interstitium (subepithelium or lamina propria) (Figure 2). Other factors may also contribute to tissue remodelling. The nature of the inflammatory and remodelling responses associated with CRS is likely to be determined by genetic and epigenetic factors [14].

Currently, CRS is considered a heterogeneous disease, with numerous predisposing factors with similar symptomatology, making it challenging to categorise CRS into clinically relevant subtypes [15]. They are traditionally classified into specific, clinical phenotypes based on the presence (CRSwNP) or the absence of nasal polyps (CRSSNP) [1]. Histologically, CRSwNP shows a predominance of interstitial oedema, whereas fibrotic remodelling of the lamina propria is the hallmark of CRSSNP [18], but there is considerable overlap in both clinical and histological presentation of disease [17]. Additional endotypic or histological phenotypes based on the presence or absence of eosinophils and cytokines are currently being investigated [16]. In this review, we will discuss only idiopathic CRS and local sinonasal inflammation where surgery can be performed.

Identification and classification of the histological features of remodelling may provide insights into why some patients with CRS do not respond to therapy, particularly those with severe asthma. One possibility is that remodelling causes irreversible damage to respiratory mucosa [19].

In this review, we summarise the current knowledge of remodelling in idiopathic CRS. The association of ECM, stromal cells, cytokines, the influence of thrombin, sinonasal inflammation, and the sinus microbiome on tissue remodelling are discussed. Moreover, the clinical implications of tissue remodelling in CRS to prognosis and response to treatment will be presented, particularly in the light of the evidence that suggests that early treatment may improve outcome.

## 2. The Role of Extracellular Matrix in Remodelling

The ECM is essential for maintaining tissue function in the presence of ongoing minor trauma or inflammation [20]. The ECM is composed of several hundred proteins, embedded in an amorphous gel-like substance made of proteoglycan [21] which allows cells to attach to the ECM. The proteoglycans are negatively charged due to the presence of sulphated

glycosaminoglycans [22]. Proteoglycans occupy a relatively large volume within the tissues and interact with positively charged molecules like cytokines and growth factors, causing the local accumulation of these molecules [23].

There are two main components of the ECM in sinus tissue: the interstitial connective tissue and the basement membrane. Collagen (types I–III, V, and XI) is a structural protein of the interstitial connective tissue that scaffolds the sinonasal submucosa. Proteoglycans (PG) such as versican, decorin, and aggrecans are macromolecules interspersed along collagen fibrils. In contrast, the basement membrane contains denser collagen (type IV), along with laminins, heparan sulphate proteoglycans (HSPGs), nidogen, and entactin [24].

The ECM is known to influence immune cell behaviour in inflamed tissues and can modulate immune function. In chronically inflamed tissue, irregularities caused by ECM altered by tissue remodelling processes can contribute to the altered immunological state of the tissues [25]. Eosinophils and collagens I, III, and V deposition in the ECM and TGF- $\beta$ -1 can be detected in the mucosa of CRS tissues. The accumulation of eosinophils can potentially damage tissue and may be an essential driver of tissue remodelling. An increase in eosinophils is observed in the sinonasal tissues of patients with CRSwNP. This increase in eosinophils encourages the production and deposition of collagen in the ECM [8, 26]. The basement membrane (BM) thickening in CRS by secretion of TGF- $\beta$  by eosinophils results in activation of fibroblasts and increased production of ECM proteins [27].

In the last decade biomarkers of ECM that play a role in remodelling in CRS, such as periostin (POSTN) and osteopontin (OPN), have been described. POSTN and OPN are matricellular proteins with cell-matrix interaction functions [28]. The first description of POSTN in sinonasal mucosa indicated that it was expressed in normal mucosa and significantly overexpressed in patients with CRSwNP [29]. A reduction in the expression of POSTN was observed following successful functional endoscopic sinus surgery (FESS), suggesting POSTN is a possible CRS biomarker that correlates with postoperative disease resolution [30].

OPN is also associated with wound repair and fibrosis generally [28]. OPN expression is markedly upregulated in CRSSNP and CRSwNP tissues compared to inferior turbinate tissues from patients without CRS disease. OPN upregulation is also detected in patients with asthma [31]. Moreover, in CRS, OPN is expressed in the nasal epithelium,

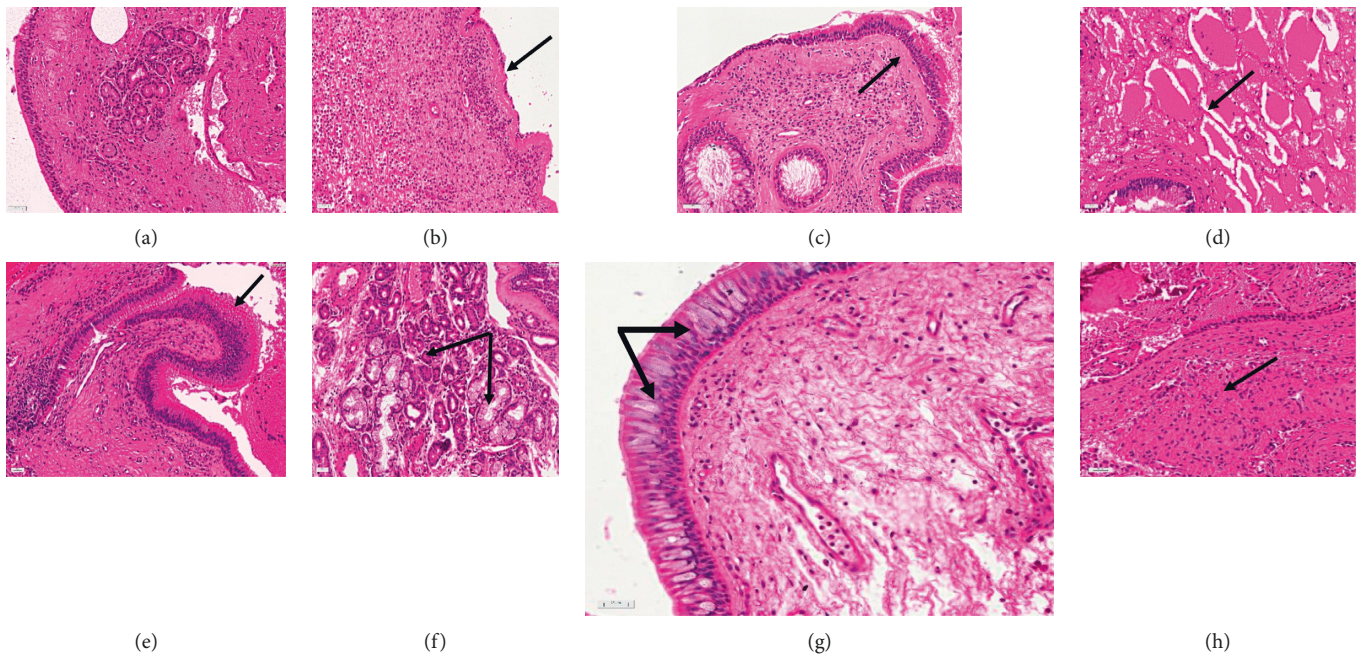


FIGURE 2: Key histological features of sinonasal mucosa remodelling during chronic rhinosinusitis (CRS). The haematoxylin and eosin-stained sections display tissue remodelling in sinonasal tissues from patients with CRS. (a) Normal mucosa, (b) epithelial denudation, (c) basement membrane thickening, (d) oedema, (e) epithelial hyperplasia, (f) glandular hyperplasia, (g) goblet cell hyperplasia, and (h) fibrosis. All images are captured at 20.05 x magnification. Black arrows indicate the different regions of interest.

submucosal glands, and the ECM, suggesting a role in tissue remodelling and ECM turnover. These ECM proteins, particularly POSTN, are associated with the increased severity of CRSwNP [32]. What remains unclear, however, is how early, in CRS pathogenesis, POSTN and OPN over-expression occurs and how these influence subsequent tissue remodelling in late-stage CRS.

### 3. Role of Cytokines in Remodelling

Cytokine expression and regulation are considered critical factors in the pathogenesis of CRS [33] (Figure 3). A distinctive pattern of cytokine production is observed during the remodelling of inflamed tissue [34]. Research has shown that some of these cytokines, like transforming growth factor (TGF- $\beta$ 1), are highly expressed in the early stages of CRSwNP [11].

Dysregulation of TGF- $\beta$ 1 is associated with increased differentiation of fibroblasts into myofibroblasts, which deposit ECM [35]. The TGF- $\beta$ 1 dimer is generated intracellularly and stored in an inactive form in the cytoplasm. This dimer needs to be activated by latency associated peptide (LAP) and latent TGF- $\beta$ 1-binding protein (LTBP-1) [36]. Integrins then activate TGF- $\beta$ 1, whose expression is increased in CRS [35, 37]. Furthermore, the differentiation of T cells to regulatory T (Treg) cells by TGF- $\beta$ 1 may lead to the specific inflammatory patterns seen in CRS [38].

TGF- $\beta$ 1 accumulates in the ECM and stroma [39]. An increase in interstitial collagen causes fibrosis and contributes to BM thickening, both of which are characteristics of CRSwNP [40]. Contrastingly, TGF- $\alpha$  may have a role in

angiogenesis, contributing to the stroma observed in CRSwNP, and with the recruitment of inflammatory cells, downstream effects such as increased epithelial proliferation and squamous metaplasia are seen [41]. Additionally, 50% of eosinophils in nasal polyps have been identified as positive for TGF- $\beta$ 1 [42]. The involvement of TGF- $\beta$ 1 in remodelling and inflammation makes this cytokine a potential target for therapy [6, 35].

The matrix metalloproteinases (MMPs), fibroblast growth factor (FGF), and bone morphogenetic factors (BMP) are all known regulators of tissue remodelling [33]. MMPs are a family of zinc-dependent and calcium-dependent endopeptidases [43] which are produced by the respiratory epithelial cells, mast cells, neutrophils, and fibroblasts [44]. MMPs play a crucial role in the breakdown of basement membranes and ECM proteins, including collagen types IV, V, VII, X, XIV, gelatin, and elastin contributing to oedema and remodelling [44]. Increased expression of MMP-9 and their regulators, tissue inhibitors of metalloproteinases (TIMPs) [40], have been found in patients with recurrent CRS [41]. Furthermore, a high TIMP-1/MMP-8 ratio is associated with an improved outcome after surgical treatment in CRSwNP, suggesting a role in remodelling [45]. This ratio correlates with disease severity and may predict a lack of response to oral corticosteroids associated with asthma [46], but this remains to be demonstrated in CRS. Metalloproteinases implicated in CRS may serve as a target for novel therapies and for evaluating prognosis [45].

Vascular endothelial growth factor (VEGF) is another cytokine that plays a critical role in vascular remodelling, causing vascular permeability and accumulation of ECM

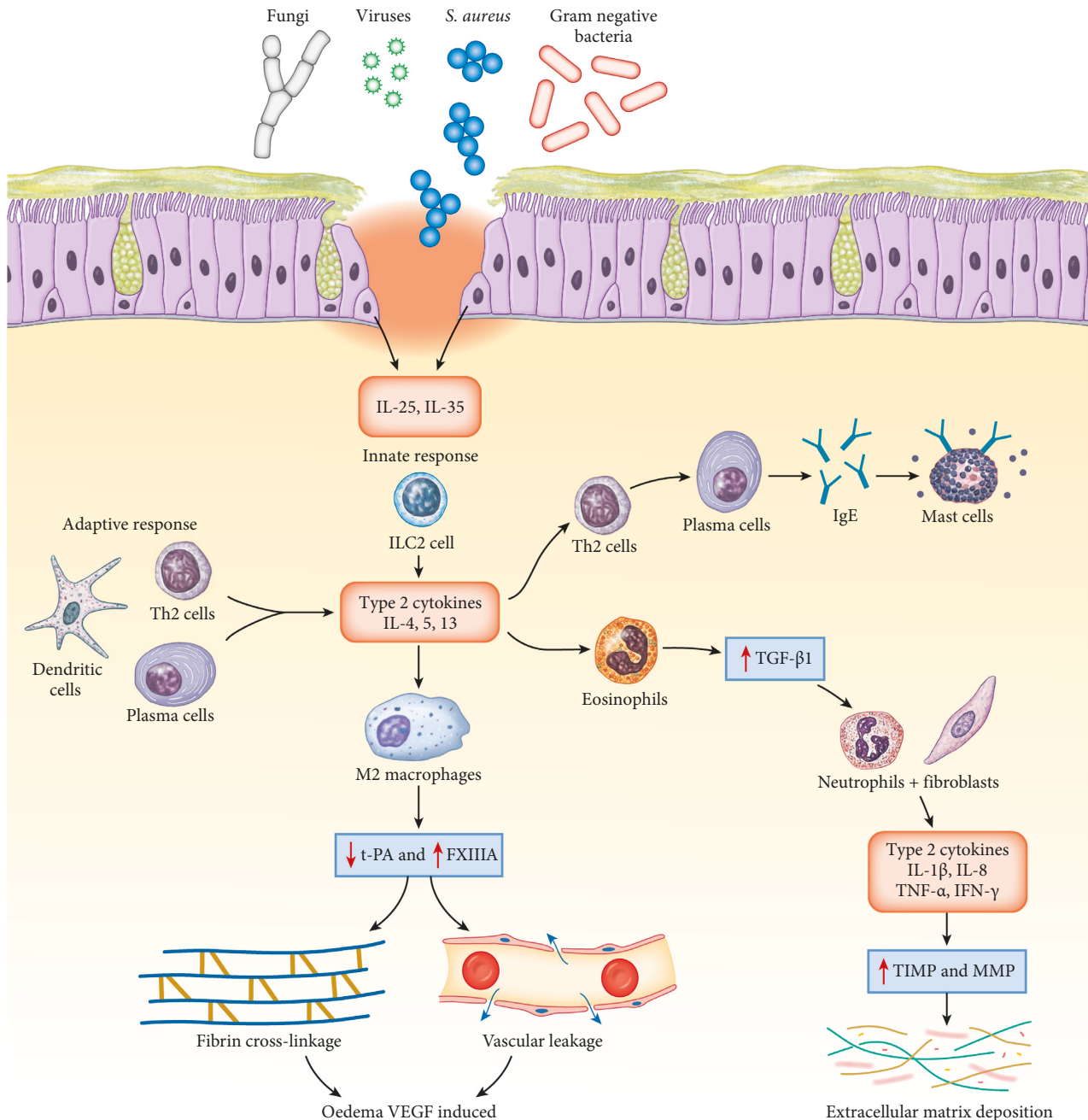


FIGURE 3: Cytokine expression in the pathogenesis of remodelling in chronic rhinosinusitis. Epithelial barrier disruption induces inflammation, initiating adaptive and innate immune response which creates a cascade of cytokines. This leads to fibrin deposition through coagulation factors like thrombin and Factor XIIIa, oedema through VEGF, and extracellular matrix deposition through TGF- $\beta$ 1. VEGF = vascular endothelial growth factor, TGF- $\beta$ 1 = transforming growth factor- $\beta$ 1, IL-1 $\beta$  = interleukin-1 $\beta$ , IL-8 = interleukin-8, TNF- $\alpha$  = tumor necrosis factor- $\alpha$ , IFN- $\gamma$  = interferon gamma, TIMP-1 = tissue inhibitor of metalloproteinase-1, MMP = metalloproteinases, and tPA = plasminogen activator.

proteins [47]. Vascular endothelial cells, fibroblasts, smooth muscle cells, macrophages, and white blood cells secrete VEGF and may contribute to the formation of oedema in polyps [48]. Prostaglandin D2 (PGD2) promotes VEGF release from NP-derived fibroblasts (NPDF) via the D-prostanoid receptor and further promotes oedema formation and angiogenesis [49].

To summarise, numerous inflammatory mediators have been implicated in the mechanism of development of nasal polyps. However, a precise mechanism of why recurrence of polyps occurs in CRSwNP associated with asthma is not

clear [47]. Perhaps, the cellular characteristics of remodelling may elucidate what contribute to early and late remodelling in CRS tissues.

#### 4. Role of Inflammatory and Stromal Cells in Remodelling

Chronic inflammation may be induced by stromal cells activating immune cells [50]. Mesenchymal-derived cells such as the fibroblasts are the most abundant stromal cells

and are implicated in the overproduction of ECM [51]. Under normal physiological conditions, fibroblasts produce the ECM constituents such as type I, III, and V collagen and fibronectin. They produce MMPs in the ECM and basement membrane comprised of collagen IV and laminin [52].

The early development of nasal polyps depends on the conversion of fibroblasts into myofibroblasts whose activity is expressed by  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) and overproduction of ECM proteins including POSTN [8]. Myofibroblasts, in turn, modulate the different components of the ECM, like the proteoglycans, elastin, and collagen, including matricellular proteins like POSTN [53]. POSTN is secreted in response to interleukins IL-4 and IL-13 [54] and is involved with subepithelial fibrosis through interactions with integrins [55].

Macrophages play a valuable role in tissue remodelling after damage through phagocytosis of damaged cells. In particular, activated macrophages (M2 type) reduce the inflammatory response and initiate angiogenesis and tissue remodelling [56, 57]. In CRS, subepithelial eosinophils and M2 type macrophages are increased significantly in early-stage nasal polyps when compared to mature polyps and normal mucosa [11].

## 5. Role of Coagulation Factors in Remodelling

Coagulation and fibrin formation occur early in response to injury. The role of the coagulation system in tissue remodelling has been examined with a particular reference to thrombin [58]. During activation of the coagulation system, thrombin promotes remodelling by secretion of VEGF from the respiratory epithelial cells [59]. Usually, airway inflammation increases vascular permeability and plasma coagulation factors exude into the extracellular space [60]. Thrombin can further stimulate the release of cytokines such as IL-6, PGE<sub>2</sub>, PDGF, and MUC5, which encourages eosinophil migration and airway permeability.

Recent studies in CRSwNP have reported excessive fibrin deposition as a result of decreased fibrinolytic activity and increased coagulation factors [61], activating thrombin [62]. Thrombin activation lowers tissue plasminogen activator (tPA) levels and upregulates Factor XIII (FXIIIa) [58]. This overproduction of FXIIIa by M2 macrophages is thought to cause remodelling of nasal polyps via fibrin deposition, plasma protein retention, and angiogenesis [61]. Moreover, thrombin-induced VEGF may be involved in the formation of recurrent nasal polyps in CRSwNP with asthma [62].

## 6. *Staphylococcus aureus* May Influence Remodelling in CRS

There is some evidence linking colonisation of the potentially pathogenic bacterium *Staphylococcus aureus* to remodelling in CRSwNP. This bacterium degrades the epithelial barrier and drives inflammation via the production of endotoxins that act as superantigens to generate a T-cell-mediated inflammatory cascade [63, 64]. Immunoglobulin E (IgE) produced by immune cells in response to staphylococcal endotoxins also has a direct effect on eosinophils [65].

These findings correlate with increased levels of IL-5 and eosinophilic cationic protein (ECP) detected in nasal polyps caused by *S. aureus* that result in remodelling [63, 66].

The lack of TGF- $\beta$  expression in nasal polyps combined with increased expression of IgE promotes mast cell degranulation and subsequent attraction of eosinophils to the site of inflammation. The lack of expression suggests decreased T-cell function [67]. Moreover, TGF- $\beta$  plays a role in the ECM metabolism by stimulating the production of TIMP-1, inhibiting the enzymatic breakdown of the ECM, and inducing a remodelled tissue in CRSwNP. The increased cysteinyl leukotriene production by mast cells further worsens the Th2-mediated inflammation [63]. Therefore, the combination of innate and acquired immunological mechanisms explains how the remodelling and an immune response occur together in the presence of *S. aureus* (Figure 4).

The persistence of *S. aureus* is also hypothesized to play a role as a potential inducer of chronicity in nasal polyps as it can reside within fibroblasts. In CRS, a dysfunctional immune barrier characterised by inflamed mucosal epithelium, atopic conditions, and obstructive sinuses may provide a platform for secondary bacterial infection and dysbiosis, leading to chronic inflammation [68]. Moreover, specific IgE antibodies to *Staphylococcus* enterotoxins have been associated with a more severe inflammatory response in nasal polyps, particularly with comorbid asthma [69]. Treating patients early with surgery may help restrict the progression and recurrence of nasal polyps as well as controlling comorbid asthma.

## 7. Clinical Implications of Tissue Remodelling in CRS

Tissue remodelling in CRS influences the chronicity and recalcitrance of disease and may be associated with comorbid asthma [9]. However, whether this tissue remodelling is reversible [9] and what impact the resulting features have on the quality-of-life indicators [70] remain unclear.

Functional endoscopic sinus surgery (FESS) generally improves clinical outcomes and remains the mainstay of treatment of CRS cases that do not respond to medical therapy [13]. It has been suggested that delaying surgical treatment may allow the disease to progress to an irreversible state [3]. A delay in FESS is associated with higher rates of asthma [71]. There is also emerging evidence to show that repeated surgical intervention may lead to more severe tissue and bone remodelling [72].

We have focused on the use of surgery to correct anatomical obstructions, but there are many systemic diseases associated with CRS where surgery may not be appropriate. For example, systemic diseases like aspirin-exacerbated respiratory disease can be the cause of or alter the prognosis of CRS, contributing to the heterogeneity that exists currently [73]. Although patients with aspirin sensitivity are medically managed with salicylates, anti-leukotriene agents, and aspirin desensitisation, recent evidence shows that sinus surgery decreases aspirin-induced reaction severity [74].

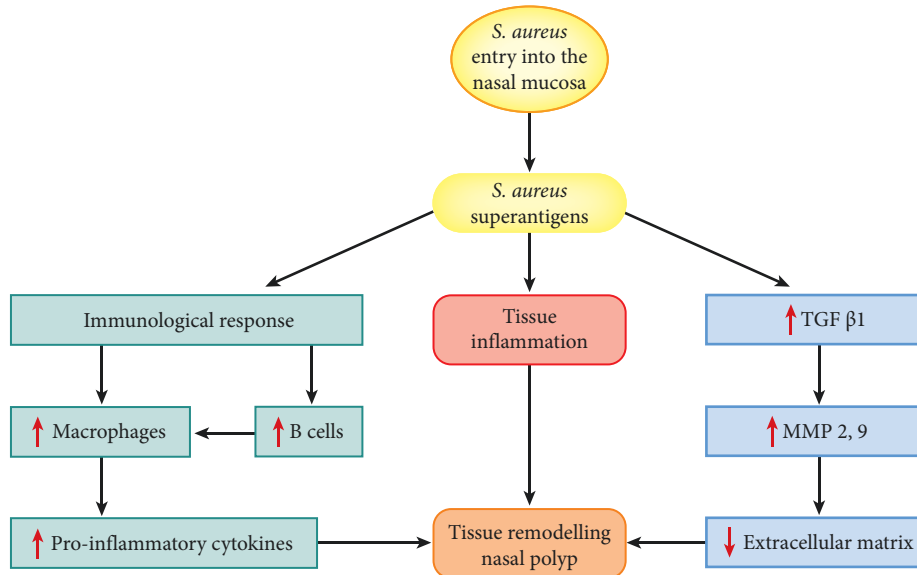


FIGURE 4: *Staphylococcus aureus* influences tissue remodelling in patients with chronic rhinosinusitis and nasal polyps. *S. aureus* drives inflammation via the production of endotoxins that act as superantigens to generate a T- and B-cell-mediated cascade. Moreover, through TGF- $\beta$  and MMP-9 and MMP-2, the extracellular matrix may be laid down inducing remodelling. TGF- $\beta$ 1 = transforming growth factor- $\beta$ 1 and MMP 2,9 = metalloproteinases 2,9.

Systemic allergy can contribute to inflammation in CRS and nonsurgical treatment may ameliorate any contribution to the overall sinonasal inflammation in a CRS patient [16, 73]. Biologics like omalizumab, an anti-immunoglobulin E (anti-IgE) monoclonal antibody, may be effective in treating CRSwNP with comorbid asthma as this systemic therapy might be useful to simultaneously control upper and lower respiratory disease [75]. Targeting key mediators of allergic inflammation such as IgE, IL-5, and IL-4/IL-13 constitutes a novel therapy in patients suffering from CRSwNP and their applicability to patients with CRSwNP refractory to standard treatment is underway [76].

The role of corticosteroids in CRS tissue remodelling is debatable. Previous research shows that the effect of corticosteroid therapy may not reduce collagen content in the basement membrane. More recently, corticosteroid therapy is thought to reverse the process of remodelling by reducing the collagen content in the basement membrane [9, 77].

Aberrant tissue remodelling has been shown to adversely affect mucociliary function [70], resulting in prolonged duration of CRS symptoms in those patients with asthma and aspirin sensitivity [27]. Evidence-based research in the lower airways may indicate that an increase in basement membrane thickness may be protective [78]. However, this finding has not been reported in the upper respiratory tract. Modulation of basement membrane may be an avenue of research with regard to targeted therapy against remodelling in CRS, based on research indicating the thickness of the basement membrane may correlate with the duration of disease [27].

## 8. Conclusions

The published literature suggests tissue remodelling occurs in CRS and distinct histological features can be used to

differentiate the current phenotypes of CRS. Various inflammatory processes contribute to persistent tissue remodelling in CRS. It remains unclear whether such remodelling is irreversible without surgical intervention or whether improved clinical outcomes after treatment are reflected at the tissue level. Investigation at a histological level aimed at controlling or reversing CRS-associated remodelling early in the disease process is warranted to enable better prediction of clinical outcomes.

## Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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## References

- [1] W. J. Fokkens, V. J. Lund, J. Mullol et al., "Epos 2012: European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists," *Rhinology Journal*, vol. 50, no. 1, pp. 1–12, 2012.

- [2] W. J. Fokkens, "Epos 2020," *Official Journal of the European and International Rhinologic Societies and of the Confederation of European ORL-HNS*, vol. 29, pp. 1–464, 2020.
- [3] C. Hopkins, J. Rimmer, and V. J. Lund, "Does time to endoscopic sinus surgery impact outcomes in chronic rhinosinusitis? Prospective findings from the national comparative audit of surgery for nasal polyposis and chronic rhinosinusitis," *Rhinology Journal*, vol. 53, no. 1, pp. 10–17, 2015.
- [4] M. S. Benninger, R. Sindwani, C. E. Holy, and C. Hopkins, "Early versus delayed endoscopic sinus surgery in patients with chronic rhinosinusitis," *Otolaryngology-Head and Neck Surgery*, vol. 152, no. 3, pp. 546–552, 2015.
- [5] M. B. Antunes, D. A. Gudis, and N. A. Cohen, "Epithelium, cilia, and mucus: their importance in chronic rhinosinusitis," *Immunology and Allergy Clinics of North America*, vol. 29, no. 4, pp. 631–643, 2009.
- [6] N. Van Bruaene and C. Bachert, "Tissue remodeling in chronic rhinosinusitis," *Current Opinion in Allergy and Clinical Immunology*, vol. 11, no. 1, pp. 8–11, 2011.
- [7] J. Bousquet, W. Jacquot, A. M. Vignola, C. Bachert, and P. Van Cauwenberge, "Allergic rhinitis☆A disease remodeling the upper airways?" *The Journal of Allergy and Clinical Immunology*, vol. 113, no. 1, pp. 43–49, 2004.
- [8] K. Radajewski, M. Wierzychowska, D. Grzanka, P. Antosik, and M. Zdrenka, "Tissue remodelling in chronic rhinosinusitis – review of literature," *Journal of Otolaryngology*, vol. 73, no. 5, pp. 1–4, 2019.
- [9] A. Bassiouni, P. G. Chen, and P.-J. Wormald, "Mucosal remodeling and reversibility in chronic rhinosinusitis," *Current Opinion in Allergy and Clinical Immunology*, vol. 13, no. 1, pp. 4–12, 2013.
- [10] J.-B. Watelet, J.-M. Dogne, and F. Mullier, "Remodeling and repair in rhinosinusitis," *Current Allergy and Asthma Reports*, vol. 15, no. 6, pp. 1–7, 2015.
- [11] J. Meng, P. Zhou, Y. Liu et al., "The development of nasal polyp disease involves early nasal mucosal inflammation and remodelling," *PLoS One*, vol. 8, no. 12, 2013.
- [12] N. Van Bruaene, K. Van Crombruggen, N. De Ruyck et al., "Inflammation and remodelling patterns in early stage chronic rhinosinusitis," *Clinical and Experimental Allergy*, vol. 42, no. 6, pp. 883–890, 2012.
- [13] T. Q. Do, H. P. Barham, P. Earls et al., "Clinical implications of mucosal remodeling from chronic rhinosinusitis," *International Forum of Allergy & Rhinology*, vol. 6, no. 8, pp. 835–840, 2016.
- [14] J. Y. Kim, D. K. Kim, M. Yu, M. J. Cha, S. L. Yu, and J. Kang, "Role of epigenetics in the pathogenesis of chronic rhinosinusitis with nasal polyps," *Molecular Medicine Reports*, vol. 17, no. 1, pp. 1219–1227, 2018.
- [15] K. Biswas, R. Cavubati, S. Gunaratna et al., "Comparison of subtyping approaches and the underlying drivers of microbial signatures for chronic rhinosinusitis," *mSphere*, vol. 4, no. 1, pp. 1–13, 2019.
- [16] J. W. Grayson, M. Cavada, and R. J. Harvey, "Clinically relevant phenotypes in chronic rhinosinusitis," *Journal of Otolaryngology-Head & Neck Surgery*, vol. 48, no. 1, pp. 1–10, 2019.
- [17] W. W. Stevens, R. J. Lee, R. P. Schleimer, and N. A. Cohen, "Chronic rhinosinusitis pathogenesis," *The Journal of Allergy and Clinical Immunology*, vol. 136, no. 6, pp. 1442–1453, 2015.
- [18] R. Pawankar and M. Nonaka, "Inflammatory mechanisms and remodeling in chronic rhinosinusitis and nasal polyps," *Current Allergy and Asthma Reports*, vol. 7, no. 3, pp. 202–208, 2007.
- [19] R. M. Rehl, A. A. Balla, R. J. Cabay, M. L. Hearp, K. B. Pytynia, and S. A. Joe, "Mucosal remodeling in chronic rhinosinusitis," *American Journal of Rhinology*, vol. 21, no. 6, pp. 651–657, 2007.
- [20] C. Bonnans, J. Chou, and Z. Werb, "Remodelling the extracellular matrix in development and disease," *Nature Reviews Molecular Cell Biology*, vol. 15, no. 12, pp. 786–801, 2014.
- [21] S. C. Cowin, "Tissue growth and remodeling," *Annual Review of Biomedical Engineering*, vol. 6, no. 1, pp. 77–107, 2004.
- [22] R. O. Hynes, "The extracellular matrix: not just pretty fibrils," *Science*, vol. 326, no. 5957, pp. 1216–1219, 2009.
- [23] E. Hohenester and J. Engel, "Domain structure and organization in extracellular matrix proteins," *Matrix Biology*, vol. 21, no. 2, pp. 115–128, 2002.
- [24] P. Lu, V. M. Weaver, and Z. Werb, "The extracellular matrix: a dynamic niche in cancer progression," *Journal of Cell Biology*, vol. 196, no. 4, pp. 395–406, 2012.
- [25] L. Sorokin, "The impact of the extracellular matrix on inflammation," *Nature Reviews Immunology*, vol. 10, no. 10, pp. 712–723, 2010.
- [26] K. Carter, H. H. Kariyawasam, and G. Xanthou, "Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: the one airway concept revisited," *Allergy*, vol. 73, no. 5, pp. 993–1002, 2017.
- [27] R. M. Rehl, A. A. Balla, R. J. Cabay, M. L. Hearp, K. B. Pytynia, and S. A. Joe, "Mucosal remodeling in chronic rhinosinusitis," *American Journal of Rhinology*, vol. 21, no. 6, pp. 651–657, 2007.
- [28] S. M. Daines, Y. Wang, and R. R. Orlandi, "Periostin and osteopontin are overexpressed in chronically inflamed sinuses," *International Forum of Allergy & Rhinology*, vol. 1, no. 2, pp. 101–105, 2011.
- [29] K. M. Stankovic, H. Goldsztein, D. D. Reh, M. P. Platt, and R. Metson, "Gene expression profiling of nasal polyps associated with chronic sinusitis and aspirin-sensitive asthma," *The Laryngoscope*, vol. 118, no. 5, pp. 881–889, 2008.
- [30] W. Zhang, G. Hubin, L. M. Endam, S. Al-Mot, A. Filali-Mouhim, and M. Desrosiers, "Expression of the extracellular matrix gene periostin is increased in chronic rhinosinusitis and decreases following successful endoscopic sinus surgery," *International Forum of Allergy & Rhinology*, vol. 2, no. 6, pp. 471–476, 2012.
- [31] X. Lu, X. H. Zhang, H. Wang et al., "Expression of osteopontin in chronic rhinosinusitis with and without nasal polyps," *Allergy*, vol. 64, no. 1, pp. 104–111, 2009.
- [32] T. Ninomiya, E. Noguchi, T. Haruna et al., "Periostin as a novel biomarker for postoperative recurrence of chronic rhinosinitis with nasal polyps," *Scientific Reports*, vol. 8, no. 1, pp. 1–10, 2018.
- [33] N. B. Sautter, K. L. Delaney, F. A. Hausman, and D. R. Trune, "Tissue remodeling gene expression in a murine model of chronic rhinosinusitis," *The Laryngoscope*, vol. 122, no. 4, pp. 711–717, 2012.
- [34] T. Nakayama, K. Hirahara, A. Onodera et al., "Th2 cells in health and disease," *Annual Review of Immunology*, vol. 35, no. 1, pp. 53–84, 2017.
- [35] W. Kou, G.-H. Hu, H.-B. Yao et al., "Regulation of transforming growth factor- $\beta$ 1 activation and expression in the tissue remodeling involved in chronic rhinosinusitis," *ORL*, vol. 74, no. 3, pp. 172–178, 2012.
- [36] D. B. Rifkin, "Latent transforming growth factor- $\beta$  (TGF- $\beta$ ) binding proteins: orchestrators of TGF- $\beta$  availability," *Journal of Biological Chemistry*, vol. 280, no. 9, pp. 7409–7412, 2005.

- [37] J. J. Worthington, J. E. Klementowicz, and M. A. Travis, "TGF $\beta$ : a sleeping giant awoken by integrins," *Trends in Biochemical Sciences*, vol. 36, no. 1, pp. 47–54, 2011.
- [38] N. Van Bruaene and C. Bachert, "Tissue remodeling in chronic rhinosinusitis," *Current Opinion in Allergy and Clinical Immunology*, vol. 11, no. 1, pp. 8–11, 2011.
- [39] S. Nemati, F. Keihanian, A. Saeidinia, and M. Bakhshaei, "Effect of bevacizumab on growth of human nasal polyposis in vitro; an off-label use of anti-angiogenic agent for nasal polyposis treatment," *Drug Design, Development and Therapy*, vol. 13, pp. 3383–3389, 2019.
- [40] H.-S. Kim, H.-A. Kim, Y.-J. Suh, S.-K. Lee, D.-H. Nahm, and Y.-M. Lee, "Eosinophil inflammation of nasal polyp tissue: relationships with matrix metalloproteinases, tissue inhibitor of metalloproteinase-1, and transforming growth factor-beta1," *Journal of Korean Medical Science*, vol. 18, no. 1, pp. 97–102, 2003.
- [41] A. Elovic and D. T. W. Wong, "Mechanisms inflammatory expression of transforming eosinophils in nasal polyps," *Current Opinion in Allergy and Clinical Immunology*, vol. 3, 2003.
- [42] I. Ohno, R. G. Lea, K. C. Flanders et al., "Eosinophils in chronically inflamed human upper airway tissues express transforming growth factor beta 1 gene (TGF beta 1)," *Journal of Clinical Investigation*, vol. 89, no. 5, pp. 1662–1668, 1992.
- [43] N. Van Bruaene and C. Bachert, "Tissue remodeling in chronic rhinosinusitis," *Current Opinion in Allergy and Clinical Immunology*, vol. 11, no. 1, pp. 8–11, 2011.
- [44] C.-C. Huang, C.-H. Wang, P.-W. Wu et al., "Increased nasal matrix metalloproteinase-1 and -9 expression in smokers with chronic rhinosinusitis and asthma," *Scientific Reports*, vol. 9, no. 1, p. 15357, 2019.
- [45] K. Kostamo, E. Toskala, T. Tervahartiala, and T. Sorsa, "Role of matrix metalloproteinases in chronic rhinosinusitis," *Current Opinion in Allergy and Clinical Immunology*, vol. 8, no. 1, pp. 21–27, 2008.
- [46] M. Bossé, J. Chakir, M. Rouabhia, L.-P. Boulet, M. Audette, and M. Laviolette, "Serum matrix metalloproteinase-9:tissue inhibitor of metalloproteinase-1 ratio correlates with steroid responsiveness in moderate to severe asthma," *American Journal of Respiratory and Critical Care Medicine*, vol. 159, no. 2, pp. 596–602, 1999.
- [47] S. Shimizu, E. C. Gabazza, T. Ogawa et al., "Role of thrombin in chronic rhinosinusitis-associated tissue remodeling," *American Journal of Rhinology & Allergy*, vol. 25, no. 1, pp. 7–11, 2011.
- [48] J. Gosepath, J. Brieger, H. A. Lehr, and W. J. Mann, "Expression, localization, and significance of vascular permeability/vascular endothelial growth factor in nasal polyps," *American Journal of Rhinology*, vol. 19, no. 1, pp. 7–13, 2005.
- [49] K. Kanai, M. Okano, T. Fujiwara et al., "Effect of prostaglandin D2 on VEGF release by nasal polyp fibroblasts," *Allergy International*, vol. 65, no. 4, pp. 414–419, 2016.
- [50] M. I. Suwara, N. J. Green, L. A. Borthwick et al., "IL-1 $\alpha$  released from damaged epithelial cells is sufficient and essential to trigger inflammatory responses in human lung fibroblasts," *Mucosal Immunology*, vol. 7, no. 3, pp. 684–693, 2014.
- [51] A. Filer, C. Pitzalis, and C. D. Buckley, "Europe PMC Funders Group Targeting the stromal microenvironment in chronic inflammation," *Current Opinion in Pharmacology*, vol. 6, no. 4, pp. 393–400, 2011.
- [52] P. Sabatelli, P. Bonaldo, G. Lattanzi et al., "Collagen VI deficiency affects the organization of fibronectin in the extracellular matrix of cultured fibroblasts," *Matrix Biology*, vol. 20, no. 7, pp. 475–486, 2001.
- [53] F. Klingberg, B. Hinz, and E. S. White, "The myofibroblast matrix: implications for tissue repair and fibrosis," *The Journal of Pathology*, vol. 229, no. 2, pp. 298–309, 2013.
- [54] Y. Yao, S. Xie, C. Yang, J. Zhang, X. Wu, and H. Sun, "Biomarkers in the evaluation and management of chronic rhinosinusitis with nasal polyposis," *European Archives of Oto-Rhino-Laryngology*, vol. 274, no. 10, pp. 3559–3566, 2017.
- [55] M. Wang, X. Wang, N. Zhang et al., "Association of periostin expression with eosinophilic inflammation in nasal polyps," *The Journal of Allergy and Clinical Immunology*, vol. 136, no. 6, pp. 1700–1703, 2015.
- [56] F. Geissmann, S. Gordon, D. A. Hume, A. M. Mowat, and G. J. Randolph, "Unravelling mononuclear phagocyte heterogeneity," *Nature Reviews Immunology*, vol. 10, no. 6, pp. 453–460, 2010.
- [57] I. G. Kong and D. W. Kim, "Pathogenesis of recalcitrant chronic rhinosinusitis: the emerging role of innate immune cells," *Immune network*, vol. 18, no. 2, pp. e6–12, 2018.
- [58] D.-Y. Kim, S. H. Cho, T. Takabayashi, and R. P. Schleimer, "Chronic rhinosinusitis and the coagulation system," *Allergy, Asthma & Immunology Research*, vol. 7, no. 5, pp. 421–430, 2015.
- [59] S. Shimizu, E. C. Gabazza, T. Ogawa et al., "Role of thrombin in chronic rhinosinusitis-associated tissue remodeling," *American Journal of Rhinology & Allergy*, vol. 25, no. 1, pp. 7–11, 2011.
- [60] T. van der Poll, "Tissue factor as an initiator of coagulation and inflammation in the lung," *Critical Care*, vol. 12, no. 6, pp. S3–S9, 2008.
- [61] T. Takabayashi, A. Kato, A. T. Peters et al., "Excessive fibrin deposition in nasal polyps caused by fibrinolytic impairment through reduction of tissue plasminogen activator expression," *American Journal of Respiratory and Critical Care Medicine*, vol. 187, no. 1, pp. 49–57, 2013.
- [62] S. Shimizu, E. C. Gabazza, T. Ogawa et al., "Role of thrombin in chronic rhinosinusitis-associated tissue remodeling," *American Journal of Rhinology & Allergy*, vol. 25, no. 1, pp. 7–11, 2011.
- [63] R. Pezato, L. Balsalobre, M. Lima et al., "Convergence of two major pathophysiologic mechanisms in nasal polyposis: immune response to *Staphylococcus aureus* and airway remodeling," *Journal of Otolaryngology - Head & Neck Surgery*, vol. 42, 2013.
- [64] K. A. Seiberling, D. B. Conley, A. Tripathi et al., "Superantigens and chronic rhinosinusitis: detection of staphylococcal exotoxins in nasal polyps," *The Laryngoscope*, vol. 115, no. 9, pp. 1580–1585, 2005.
- [65] C. Bachert and N. Zhang, "Chronic rhinosinusitis and asthma: novel understanding of the role of IgE 'above atopy'," *Journal of Internal Medicine*, vol. 272, no. 2, pp. 133–143, 2012.
- [66] D. Wu, J. Wang, and M. Zhang, "Altered Th17/Treg ratio as a possible mechanism in pathogenesis of idiopathic membranous nephropathy," *Cytokine*, vol. 141, 2021.
- [67] N. Van Bruaene, C. A. Pérez-Novo, T. M. Basinski et al., "T-cell regulation in chronic paranasal sinus disease," *The Journal of Allergy and Clinical Immunology*, vol. 121, no. 6, pp. 1435–1441, 2008.
- [68] M. Mahdavinia, A. Keshavarzian, M. C. Tobin, A. L. Landay, and R. P. Schleimer, "A comprehensive review of the nasal microbiome in chronic rhinosinusitis (CRS)," *Clinical and Experimental Allergy*, vol. 46, no. 1, pp. 21–41, 2016.



- [69] R. Pezato, L. Balsalobre, M. Lima et al., "Convergence of two major pathophysiologic mechanisms in nasal polyposis: immune response to *Staphylococcus aureus* and airway remodeling," *Journal of Otolaryngology - Head & Neck Surgery*, vol. 42, 2013.
- [70] H. P. Barham, J. L. Osborn, K. Snidvongs, N. Mrad, R. Sacks, and R. J. Harvey, "Remodeling changes of the upper airway with chronic rhinosinusitis," *International Forum of Allergy & Rhinology*, vol. 5, no. 7, pp. 565–572, 2015.
- [71] M. S. Benninger, R. Sindwani, C. E. Holy, C. Hopkins, and F. Orl-hns, "Early versus delayed endoscopic sinus surgery in patients with chronic rhinosinusitis," *Otolaryngology-Head and Neck Surgery*, vol. 152, no. 3, pp. 546–552, 2015.
- [72] S. H. Cho, K. S. Shin, Y. S. Lee et al., "Impact of chronic rhinosinusitis and endoscopic sinus surgery on bone remodeling of the paranasal sinuses," *American Journal of Rhinology*, vol. 22, no. 5, pp. 537–541, 2008.
- [73] M. W. Ryan, "Diseases associated with chronic rhinosinusitis: what is the significance?" *Current Opinion in Otolaryngology & Head and Neck Surgery*, vol. 16, no. 3, pp. 231–236, 2008.
- [74] E. Jerschow, M. L. Edin, Y. Chi et al., "Sinus surgery is associated with a decrease in aspirin-induced reaction severity in patients with aspirin exacerbated respiratory disease," *The Journal of Allergy and Clinical Immunology: In Practice*, vol. 7, no. 5, pp. 1580–1588, 2019.
- [75] T. Bidder, J. Sahota, C. Rennie, V. J. Lund, D. S. Robinson, and H. H. Kariyawasam, "Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together-a real life study," *Rhinology journal*, vol. 56, no. 1, pp. 42–45, 2018.
- [76] N. Tsetos, J. K. Goudakos, D. Daskalakis, I. Konstantinidis, and K. Markou, "Monoclonal antibodies for the treatment of chronic rhinosinusitis with nasal polyposis: a systematic review," *Rhinology journal*, vol. 56, no. 1, pp. 11–21, 2018.
- [77] C. Mastruzzo, L. R. Greco, K. Nakano et al., "Impact of intranasal budesonide on immune inflammatory responses and epithelial remodeling in chronic upper airway inflammation," *The Journal of Allergy and Clinical Immunology*, vol. 112, no. 1, pp. 37–44, 2003.
- [78] M. Milanese, E. Crimi, A. Scordamaglia et al., "On the functional consequences of bronchial basement membrane thickening," *Journal of Applied Physiology*, vol. 91, no. 3, pp. 1035–1040, 2001.