

## Sinusitis & Bone: Review

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### Abstract

Over the past few years, a lot of research has been done to understand the role of osteitis, or inflammation involving bone for disease recalcitrance in chronic rhinosinusitis (CRS). This review article will discuss the current understanding of osteitis in CRS, including pathophysiology, diagnostic methods, clinical significance, and treatment modalities.

**Keywords:** role of osteitis, pathophysiology, diagnostic methods, clinical significance.

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## INTRODUCTION

Sinusitis is defined as an inflammatory disorder of the paranasal sinuses. The American Academy of Otolaryngology-Head and Neck Surgery has classified disease as acute, subacute, chronic, and acute exacerbations of chronic rhinosinusitis [1].

Most cases of acute bacterial sinusitis are secondary to viral upper respiratory infection or nasal inflammation, referred as rhinosinusitis. When the symptoms persist for more than 12 weeks with no complete resolution, it is called as chronic rhinosinusitis. It responds poorly to intensive medical and surgical therapies. Osteitis has been reported as part of the pathophysiological process of chronic rhinosinusitis (CRS) [1, 2]. The prevalence of bony involvement in CRS is around 51%, with a higher prevalence in patients with previous sinus surgery (76%) than patients with primary surgery (36%). Osteitis is also associated with tissue eosinophilia, nasal polyps, and serum eosinophilia [3]. In experimentally induced sinusitis with *Pseudomonas aeruginosa*, Bolger et al. demonstrated bone changes occur as early as 4 days after infection. These changes included a coordinated osteoclasts and appositional bone formation adjacent to the sinus, as well as subsequent intramembranous bone formation [4].

Clinical experience with computed tomography and nasal endoscopy has demonstrated that the bone may undergo reabsorption or even perforation

during acute or early-stage chronic rhinosinusitis. It was noted that following sinus surgery, disease persisted at one or more localized sites, despite appropriate medical therapy and postoperative debridement, resolved on removing the underlying bone [5].

These clinical findings led to our interest in further evaluating the correlation between the underlying bone and chronic sinusitis. This paper focuses on understanding the etiopathogenesis through animal and human models, methods to diagnose the osteitic bone, clinical significance of these findings.

## PATHOPHYSIOLOGICAL MECHANISMS

Osteitis can be defined as inflammation of bone. Other terms used to describe osteitis include hyperostosis, bony involvement, new bone formation, neo-osteogenesis and chronic osteomyelitis. Osteitis is the bony thickening of sinus walls present in chronic rhinosinusitis. These osteitic bones potentially serve as a nidus for inflammation.

The mechanism of osteitis in CRS is still unclear. The etiopathogenesis may be compared with that of bacterial biofilms in periodontal disease [9]. It is possible that bacteria within the mucosa can stimulate the underlying bone to release inflammatory mediators, prostaglandins, and leukotrienes that stimulate

osteoclast-mediated removal and osteoblast-mediated replacement to bring about bony remodeling.

At the molecular level, osteoblast and osteoclast activity are actively regulated by members of the transforming growth factor (TGF)- $\beta$  superfamily. In a mouse model of TGF- $\beta$  overexpression, researchers have demonstrated increased bone matrix formation. The bone morphogenetic protein (BMP) family of cytokines are members of the TGF- $\beta$  superfamily, and are isomorphic to TGF- $\beta$ . Upregulation of BMP and BMP in the sinonasal tissues have been observed in a mouse model of CRS. Inflammatory cytokines outside of the TGF- $\beta$  superfamily may also promote bony remodeling. These tissue remodeling changes become irreversible, leading to the development of recalcitrant CRS. Understanding the molecular triggers for bony remodeling may lead to development of specific inhibitors of these molecules to prevent the process from occurring [7].

Also as demonstrated by the aforementioned studies, inflammation within the bone may then travel through Haversian canals to involve the rest of the paranasal sinuses [8]. This hypothesis can be correlated with clinical observation that debridement of only the overlying areas of mucosal hypertrophy frequently results in persistent disease, whereas debridement of the underlying bone often resolves areas of persistent disease in postoperative patient.

## HISTOLOGIC STUDIES IN ANIMAL MODELS

Most commonly used experimental animal model, to assess the bone and mucosal inflammation is rabbit models. These studies show bone involvement as early as two weeks after the rhinosinusitis induction process has begun and persisting at varying intensities, for up to 13 weeks. The most commonly described findings of bone inflammation are: periosteal thickening, inflammatory infiltrate, increased osteoclastic and osteoblastic activity, new bone formation, and eventually fibrosis [9, 10]. Histomorphometric studies demonstrated the evidence of active bony remodeling in the ethmoid bone of patients with chronic rhinosinusitis. These findings were usually detected in patients who had undergone primary sinus surgery and in those who had previous surgery [11]. Perloff *et al.*, demonstrated that in a *Pseudomonas*-induced sinusitis, inflammation could spread to noninvolved, noninfected sinus bone through the Haversian canals, due to osteoclastic resorption and increased vascularity thus resulting in widening of the spaces. Similar results were demonstrated when the rabbits were infected with *Pseudomonas* and *Staphylococcus aureus* [5].

## CLINICAL STUDIES OF OSTEITIS IN CHRONIC RHINOSINUSITIS

Rabbit model is a poor disease correlate of human chronic rhinosinusitis. It is a multifactorial disease, making it difficult to replicate the various inflammatory, environmental, host and genetic aspects in an animal model. The chronic process of paranasal sinus inflammation is artificially inoculated into the sinus in an animal model. This methodology of surgical intervention during inoculation and sampling predisposes to infection and may therefore be the cause of the bony changes itself. Due to these limitations, findings from the animal studies couldn't be extrapolated to clinical scenarios.

Giacchi *et al.*, performed histomorphometric studies on the ethmoid bone of 19 patients who underwent endoscopic sinus surgery for chronic rhinosinusitis. Eighteen of 19 patients demonstrated some degree of bony resorption and bony remodeling. Catalano *et al.*, in a 6-month prospective study attempted to determine the incidence of reactive bone in the surgical specimens of patients with chronic rhinosinusitis who underwent Functional Endoscopic Sinus Surgery (FESS). The determination of reactive bone was made through light microscopy. Results showed that 53% of the cases showed reactive bone of increased osteoid and woven nonlamellar bone formation [13].

## DIAGNOSTIC METHODS

There is no gold standard diagnostic test for osteitis. Histology is considered the most accurate, and several grading systems have been proposed. However, histology is impractical as a routine diagnostic method due to need for biopsy or surgery. During surgery, osteitis may be detected by direct clinical observation of removed bone and has been described having a "honeycomb-like" appearance. Less invasive methods have been developed to identify osteitis including methodical analysis of computed tomography (CT) of the sinuses and single photon emission CT (SPECT). CT is currently the preferred diagnostic method of choice. Lee *et al.*, advocated a method by which osteitis is diagnosed based on thickness of bony partitions in the maxillary, ethmoid and sphenoid sinuses (Table-1). A more recent study utilized both bony thickness and pattern of bony involvement in each sinus to calculate an aggregate score, termed the Global Osteitis Scoring Scale (Table-2). Limitation with CT is that in certain scenarios soft woven bone shows relative hypodensity compared with mature new bone formation, but both radiographically represent osteitis. Thus radiographic findings should be correlated with clinical picture to establish a diagnosis of osteitis [14].

**Table-1: CT Grading of Osteitis – Lee et al., [15]**

Grade (per sinus)	Bony Thickness (mm)
Not significant	<3
Mild	3
Moderate	4-5
Severe	>5

CT= Computed tomography

**Table-2: Global Osteitis Score [16]**

Grade	Sinus wall involvement (%)	Thickness (mm)	Scoring (unilateral)	
1	<50	<3	Frontal	5
2	<50	3-5	Anterior ethmoid	5
3	<50	>5	Posterior ethmoid	5
3	<50	<3	Maxillary	5
4	<50	3-5	Sphenoid	5
5	<50	>5	Total	25

Severity determination (bilateral score): not significant= &lt;5; Mild=5-20; moderate= 20-35; and severe=&gt;35

## CLINICAL SIGNIFICANCE

The prevalence of osteitis is a confounding factor with respect to treatment of CRS. Use of minimally invasive sinus technique should be limited as it leaves behind osteitic ethmoid bone partitions which act as a nidus for infection. FESS, with the complete removal of the bony partitions within diseased areas, is an accepted procedure to eradicate a persistent source of inflammation. FESS also improves the depth of penetration of topical medications and anti-inflammatory agents into diseased mucosa within the paranasal sinuses [13]. Systemic steroids are given routinely in patients with nasal polyposis and chronic hyperplastic rhinosinusitis. Alternatively, local therapies such as nebulized steroids and topical antifungal agents have been used to combat local mucosal inflammation, and oral agents such as leukotriene inhibitors and low-dose macrolide therapy have been tried systemically. Further research is needed to find an effective anti-inflammatory agent with tolerable side effects that can be used for long periods.

Due to the similarity with osteomyelitis, long-term intravenous antibiotics have been administered to treat persistent inflammation and infection within the sinus mucosa. However this mode of treatment is unaccepted as the presence of bacteria within the bone of sinuses is yet to be proved. Limiting the bacterial count in the overlying mucosa remains an important step in controlling the underlying inflammation. This treatment is best done with the aid of endoscopically derived aerobic, anaerobic, and fungal cultures. The length of treatment is subject to interpretation, although many physicians believe that a minimum of 3 weeks of oral antibiotics is needed for chronic rhinosinusitis [17]. Further studies are needed to determine the effects of long-term systemic antibiotics on the inflammation within the bone and to determine the optimal length of therapy.

## CONCLUSION

Clinical implication of effect of sinusitis on bone is yet to be explored. Despite multiple existing studies, the precise mechanism and pathophysiology of development of osteitis in CRS remains unknown. Molecular markers and cell signaling pathways are receiving increasing attention, and osteitis may be associated with certain identifiable markers, whose determination may provide opportunities for future therapeutic targets that can be exploited to prevent the process from occurring or progressing. Newer techniques may allow for more precise surgical therapies. An ultrasonic bone aspirator [18] has been utilized in rhinologic applications to remove bone in a mucosal sparing fashion, and has been reported to exhibit minimal heat transmission and collateral soft tissue damage. Future long term studies are needed to validate the findings and improve our ability to treat bone involvement in chronic rhinosinusitis.

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