Chronic rhinosinusitis (CRS) is a multifactorial and highly heterogeneous upper airway disease that affects approximately 12% of the general population. There is increasing evidence supporting the impact of osteitis on the pathophysiology of CRS. Osteitis is frequently observed in patients with CRS, and is associated with severe sinonasal inflammation and recalcitrant cases. The overlying inflammatory sinonasal mucosa plays a critical role in the initiation of osteitis; however, the underlying molecular mechanisms and functional significance remain unclear. Increasingly many studies have suggested that immune cells play a crucial role in the bone remodeling process in CRS. The purpose of this review is to summarize the current state of knowledge regarding the specific role of sinonasal inflammation in bone remodeling in CRS patients.

Keywords. Osteitis; Chronic Rhinosinusitis; Inflammation; Osteoblasts; Osteoclasts; Cytokine

INTRODUCTION

Chronic rhinosinusitis (CRS) is a multifactorial and highly heterogeneous upper airway disease that affects approximately 12% of the general population. CRS also significantly affects the quality of life of individuals with the disease. CRS is classified into two major subtypes based upon its phenotypic manifestation: CRS without nasal polyps (CRSsNP) and CRS with nasal polyps (CRSwNP) [5]. The inflammatory patterns of CRSsNP and CRSwNP are known to be different. CRSsNP is predominantly characterized by neutrophilic inflammation with increased levels of T helper (Th) 1 cytokines [1,6]. CRSwNP is often characterized by eosinophilic, immunoglobulin E production, and Th2 cytokine expression in Western countries [7]. In contrast, only approximately half of patients with CRSwNP in Asian countries demonstrate eosinophilic inflammation with Th2 cells [8-10]. Non-eosinophilic CRSwNP commonly demonstrates Th1/Th17-predominant immune responses [11].

Increasing evidence supports the impact of osteitis on the pathophysiology of CRS [12]. Osteitis is often observed in CRS patients, and is associated with disease severity and recalcitrant cases [13]. Osteitis is defined as the process of new bone formation and bone remodeling inside the paranasal sinuses, and is characterized by periosteal thickening, new woven bone formation, bone resorption, and fibrosis [14,15]. However, the causes and pathogenesis of osteitis in CRS remain incompletely understood. The purpose of this review is to summarize the current state of knowledge regarding the specific role of sinonasal inflammation in bone remodeling in CRS patients.

INCIDENCE OF OSTEITIS

The exact prevalence and incidence of osteitis vary depending on the evaluation criteria. Osteitis was identified in 39.6% of CRS patients who underwent primary surgery [16]. Lee et al. [15] reported the presence of osteitis in 36%–53% of CRS pa-
tients based on either the radiographic criterion of bony thickening or pathologic findings. Snidvongs et al. [17] found evidence of osteitis in around 51% of CRS patients, with a higher prevalence in patients with prior sinus surgery (76%). Georgalas et al. [18] reported that 33% of primary CRS patients showed signs of osteitis. Bony changes were present in 75% of patients who underwent prior sinus surgery [18].

**DIAGNOSTIC METHODS**

Histology is considered to be the most precise method of diagnosing osteitis, and several grading systems for osteitis have been proposed [19-21]. The histologic indicators of osteitis include periosteal thickening, increased activity of osteoblasts and osteoclasts, woven bone formation, and fibrosis [14]. Although histology provides an accurate way to diagnose osteitis, radiologic studies are the most generally used investigations. Computed tomography (CT) is currently the imaging modality of choice for evaluating CRS due to its superior detail for imaging bone and its excellent sensitivity and specificity with regard to detecting periosteal thickening. CT scans were first used by Biedlingmaier et al. [20] to diagnose osteitis, and CT findings were found to be correlated with histologic findings in patients with advanced-grade disease. Cho et al. [19] demonstrated radiologic and histopathologic evidence of bony changes in CRS patients. Furthermore, Lee et al. [15] measured the thickness of bony partitions in the maxillary, ethmoid, and sphenoid sinuses to determine the severity and radiologic evidence of osteitis. Georgalas et al. [18] proposed the Global Osteitis Scoring Scale (GOSS), which generates an aggregate score depending on bony thickness and the pattern of bony involvement in each sinus. The GOSS score was found to be correlated with the Lund-Mackay score, duration of symptoms, and prior surgery.

**DISEASE SEVERITY AND OUTCOMES**

Osteitis has been demonstrated to be associated with disease severity. Previous studies documented higher overall CT scores in patients with osteitis than in those without osteitis [15,22]. A number of factors had significantly higher prevalence in patients with osteitis, including nasal polyps, a history of prior surgery, increased mucosal inflammation, and worse treatment outcomes [22,23]. The ethmoid sinus was the predominant site of osteitis in eosinophilic CRSwNP, whereas non-eosinophilic CRSwNP showed maxillary predominance based on CT findings [24,25].

**BONE CELLS**

Bone remodeling is the process by which mature bone is continually removed by resorption and new bone is formed [26]. Osteoblasts play a dominant role in this process and also control osteoclast activity via the release of soluble mediators [27,28]. Ishino et al. [29] established an osteoblast cell model from the ethmoid sinus from patients with CRS, in which they were able to culture and differentiate cells from explanted sinus bone that expressed extracellular matrix proteins. Stevens et al. [30] found a fundamental phenotypic difference in adhesion and mineralization between osteoblasts from patients with CRS and osteoblasts from controls. These findings suggest that identifying the immunological and molecular mechanisms of osteoblast activation can be used to better elucidate the bone remodeling process in an inflamed microenvironment. Further studies are needed to explore possible causal links between overlying mucosal inflammation and adjacent bone structures since bone cells play a central role in the bone remodeling process.

**PATHOPHYSIOLOGY AND MOLECULAR MECHANISMS**

**Eosinophilic remodeling**

The overlying inflammatory sinonasal mucosa plays a critical role in the initiation of osteitis; however, the molecular mechanisms and functional significance remain unclear. Increasingly many studies have suggested that immune cells are crucial for bone remodeling in CRS patients. Snidvongs et al. [17] found that osteitis was associated with tissue and serum eosinophilia in both patients with and without prior surgery. Mehta et al. [31] reported that blood eosinophil levels in patients were directly correlated with sinus mucosal thickening and associated with osteitis. Gunel et al. [32] reported that high levels of P-glycoprotein (P-gp) were linked with an increased osteitis burden as measured by the Kennedy Osteitis Score and the GOSS. P-gp, also referred to as multidrug resistance protein, functions as an adenosine triphosphate-dependent efflux pump and is expressed in a variety of cell types, including both immune cells and epithelial cells. Patients with CRSwNP and eosinophilic CRSwNP had higher expression levels of P-gp in nasal mucosa than healthy controls [33-35]. It was demonstrated that P-gp exhibited immunomodulatory activity and affected the secretion of inflammatory cytokines and chemokines [36]. Bleier et al. [37] docu-
mented that P-gp directly promoted Th2-associated cytokine secretion into the local tissue microenvironment. Thus, the strong association of eosinophils with osteitic bone may provide a compelling explanation for new bone formation in CRS patients. The ability of eosinophils to secrete various proinflammatory mediators suggests that these cells have the possibility to directly impact osteogenic cells [38-40].

The role of cytokines and growth factors
Tuszynska et al. [41] found a significant upregulation of interleukin (IL)-6, IL-11, and tumor necrosis factor (TNF)-α expression levels in CRS patients with osteitis. Wang et al. [42] explored the significance of transforming growth factor (TGF)-β/Smad signaling in osteitis in CRS with and without nasal polyps. Gunel et al. [43] evaluated tissue samples obtained from osteitic bone and the overlying mucosa in CRSwNP patients and healthy controls (n = 8 per group). They found that growth differentiation factor (GDF)-5 and exostosin glycosyltransferase 1 were significantly upregulated and positively correlated with mucosal eosinophilic inflammation in CRS patients with osteitis. In addition, a correlation was found between mucosal eosinophil count and GDF-5 levels. Those findings suggest that eosinophilic inflammation may trigger bony changes via GDF-5. GDF-5 is a member of the bone morphogenetic protein (BMP) family, which belongs to the TGF-β superfamily and plays a critical role in bone formation [44]. Some members of the BMP family were shown to be upregulated or downregulated in a mouse model of eosinophilic CRS [45]. However, little is known regarding the specific role of BMP family members in CRS patients with osteitis.

In a more recent study, Wu et al. [46] assessed mucosal samples obtained from sites of osteitic bone in 10 patients with CRSwNP and 10 healthy controls. The authors found that pro-osteoblastic expression of BMP-7, BMP-9, and their receptors (BMPRIA and BMPR2) were downregulated in CRSwNP, indicating a generalized decrease in pro-osteoblastic activity. Furthermore, downregulated BMP signaling was significantly associated with increased osteitis in CRSwNP.

Recently, Oue et al. [47] evaluated sinonasal bone and mucosal samples from 38 patients with CRS with and without neo-osteogenesis and nine control patients. In their study, the expression of IL-13, CCL13, colony-stimulating factor 3, integrin alpha M, alkaline phosphatase liver/bone/kidney, and TNF-α were significantly upregulated in CRS patients with neo-osteogenesis when compared with control patients and CRS patients without neo-osteogenesis. Moreover, a significant positive correlation was found between GOSS scores and IL-13 mRNA levels. A positive correlation was found between IL-13 concentrations and the degree of mineralization in primary osteoblasts isolated from CRS patients. Silfversward et al. [40] showed that IL-4 and IL-13 enhanced markers of differentiated osteoblastic activity, including stimulation of collagen secretion, alkaline phosphatase expression, and mineralization. Furthermore, the expression of IL-13 presented a significant positive correlation with osteogenesis-related gene sets in the human CRS transcriptome [48]. Shi et al. [49] demonstrated that IL-13 promoted the expression of runt-related transcription factor 2 (RUNX2) in human bronchial epithelial cells. Moreover, elevated levels of IL-13 and IL-17A in CRS patients with neo-osteogenesis were found to be related to osteoblast differentiation through the induction of RUNX2 [50]. RUNX2, also known as core-binding factor subunit alpha-1, is an essential transcription factor for osteoblast development and differentiation [51]. It acts throughout the induction, proliferation, and maturation of osteoblasts and regulates the expression of many osteoblast genes [52,53]. RUNX2 expression was detected in cells around new bone surfaces in CRS sinonasal specimens, and a significant positive correlation was found between GOSS scores and RUNX2-positive cells [50].

The role of the RANKL/RANK/OPG axis
The differentiation of bone-resorbing cells is centered on the key osteoclastogenic cytokine receptor activator of nuclear factor-κB ligand (RANKL; also known as TNF ligand superfamily member 11). RANKL has two receptors, a signaling receptor (RANK) and a decoy receptor (osteoprotegerin [OPG]); both belong to the TNF superfamily [54,55]. Various studies have demonstrated that RANKL is mainly produced by T cells, B cells, and basophils [56-58]. Kong et al. [25] assessed mucosal samples from 71 patients with CRS and 12 healthy subjects to investigate the expression of RANKL and analyzed the correlation between RANKL expression and osteitis. RANKL expression was upregulated in patients with CRS and was associated with clinical osteitis and disease severity. Immunohistochemical staining showed that RANKL-positive cells were significantly more densely distributed in the periosteum of CRS tissue than in control tissue. Multiple inflammatory mediators were also positively correlated with RANKL protein expression. Furthermore, RANKL/OPG expression was found to be higher in recurrent cases than in primary cases, showing that RANKL is related to osteitis in cases of CRS with a poor prognosis. In contrast, OPG protein expression was lower in recurrent cases than in primary cases.

Bone is a highly dynamic tissue that is remodeled in response to diverse inflammatory stimuli (Fig. 1). More studies are needed to elucidate the impact of proinflammatory cytokines and growth factors produced by immune cells on bone biology. A thorough confirmation and complete understanding of the role that immune cells play in bone remodeling in CRS are essential to facilitate the ongoing search for improved therapeutics.

**ROLE OF BACTERIA IN OSTEITIS**

To date, few studies have reported the role played by bacteria in osteitis. Huang et al. [59] performed a retrospective study to evaluate predictive factors of neo-osteogenesis in CRS. The main fo-
Cus of that study was the evaluation of bacterial cultures in these groups, which revealed that the presence of *Pseudomonas aeruginosa* was strongly predictive of neo-osteogenesis. In contrast, the presence of *Staphylococcus aureus* and coagulase-negative *S. aureus* in the sinuses was not associated with development of neo-osteogenesis. That study was the first to demonstrate that bacteriological factors predicted neo-osteogenesis. In agreement with previous studies, Huang et al. [59] also demonstrated that prior surgery and Lund-Mackay scores were independent predictors of neo-osteogenesis. In a more recent study, Karempelis et al. [60] found that the presence of *P. aeruginosa* was not associated with neo-osteogenesis in CRS patients with or without cystic fibrosis. That result is in contrast to a previous report. In agreement with a prior study, neither *S. aureus* nor coagulase-negative *S. aureus* affected neo-osteogenesis in patients with CRS.

Dong et al. [61] investigated the association between bacterial biofilms and osteitis status in CRS patients. In their study, 84.8% of the bones underlying mucosa with biofilms had histopathologic and radiologic evidence of osteitis. Furthermore, the CRS patients who had previously undergone surgery had significantly higher bacterial biofilm and osteitis scores than patients undergoing primary surgery. However, the specific role of bacterial biofilms in the pathogenesis of CRS with osteitis has yet to be revealed [62].

**APPLICATIONS OF ANIMAL MODELS FOR ELUCIDATING MOLECULAR MECHANISMS AND TESTING NOVEL THERAPEUTIC CANDIDATES**

Animal models have strongly contributed to the explanation of mechanisms involved in CRS pathophysiology and the development of novel therapies [63-65]. Rabbit models have been used to elucidate bony changes in CRS in several studies. Perloff et al. [66] identified the histological changes that occurred in bone and in the overlying mucosa in an experimentally induced CRS model. Khalid et al. [67] showed that rabbits inoculated with bacterial organisms (*P. aeruginosa* and *S. aureus*) developed chronic sinusitis and had evidence of osteomyelitis. Clear evidence was found of an inflammatory reaction associated with fibrosis, periosteal reaction, hyperplastic osteoblasts, osteoclastic resorption, and Haversian canal changes. Similarly, Dong et al. [68] evaluated bone remodeling at 4, 8, and 12 weeks after intranasal inoculation of *S. aureus*. The presence of osteitis was identified by changes in periosteal thickening, osteoblastic and osteoclastic activity, and woven bone formation in sections used for histologic scoring.

Murine models have been used to study the pathophysiology of CRS in several recent studies [69-75]. Mice have several advantages over rabbits as a model of CRS, including the availability of reagents to explore immunological responses and the availability of many knockout and transgenic models. Other advantages of the mouse model include the small size of mice, which significantly reduces the amounts of drugs or chemicals needed for experiments [76,77]. In a recent study, our research group [48] found histologic and radiographic evidence of new bone formation or neo-osteogenesis in an eosinophilic CRS model and explored the relationship between IL-13 and RUNX2. In that study, RUNX2-immunoreactive osteoblasts were significantly increased and positively correlated with bone thickness and IL-13 expression in experimental mice. Furthermore, the administration of resveratrol (known to be a SIRT1 activator) reduced mucosal inflammation [78,79] and new bone formation, suggesting the applicability of this murine model for investigating the efficiency of drugs targeting CRS patients with neo-osteogenesis. In a recent study, Kong et al. [25] showed that anti-RANKL treatment inhibited mucosal inflammation and related osteitis in a murine model of CRS. Thus, this murine model can be used to elucidate the mechanism of new bone formation in CRS and might open new avenues towards the identification of novel therapeutic strategies.
CONCLUSION

Osteitis is associated with severe mucosal inflammation and revision sinus surgery, but its role in CRS pathophysiology remains poorly understood. Immune cells play a critical role in bone remodeling in CRS patients. Therefore, a detailed knowledge of the involvement of the immune system, and the cytokines and immune signals that mediate bone biology in CRS, will contribute significantly to drug development.

CONFLICT OF INTEREST

Hyun Woo Shin is an editorial board member of the journal but did not involve in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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ORCID

Roza Khalmuratova  https://orcid.org/0000-0002-8518-4034
Hyun-Woo Shin  https://orcid.org/0000-0002-4038-9992

AUTHOR CONTRIBUTIONS

Conceptualization: all authors. Funding acquisition: HWS. Project administration: HWS. Visualization: RK. Writing—original draft: RK. Writing—review & editing: HWS.

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