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RHINOSINUSITIS (J MULLOL, SECTION EDITOR)

Osteitis in Chronic Rhinosinusitis

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Abstract

Purpose of Review Osteitis is recognized as a common factor in recalcitrant chronic rhinosinusitis (CRS). There is evidence for the association of osteitis with revision surgeries and CRS severity, in terms of higher Lund-Mackay scores. This is a narrative review on the osteitis in CRS patients.

Recent Findings Evidence to date is inconclusive with regard to the etiology and pathogenesis of this bony thickening. Histopathology of osteitis in primary CRS is likely a process of neo-osteogenesis and bone remodeling. For better understanding, various associating factors have been studied including an inflammatory pattern of rhinosinusitis. Recent studies have associated osteitis with nasal polyps and tissue eosinophilia with the increase in periostin expression and P-glycoprotein mucosal expression. There is no association of osteitis to symptoms or quality of life. Osteitis is an outcome of neo-osteogenesis rather than inflammatory processes in CRS patients without a prior history of surgery. While CT has become a staple in osteitis assessment, the standards for grading osteitic severity remain in an experimental stage. There is no association between the presence or severity of osteitis at the time of surgery and clinical outcomes at 1 year after surgery.

Summary This review provides a comprehensive overview of the pathogenesis, epidemiology, and correlation with clinical and biological factors of osteitis in CRS patients.

Keywords Osteitis · Rhinosinusitis · Nasal polyps · Endoscopic sinus surgery · Histopathology · Computed tomography

Introduction

The term osteitis has been used to describe bony thickening of sinus walls present in chronic rhinosinusitis (CRS). As opposed to the term osteomyelitis, osteitis describes the bone involvement of sinus walls without bone marrow (with the exception of the frontal sinus) [1]. Since the very first detection of the bone involvement in early studies, contemporary studies have now progressed to recognizing osteitis as a common factor in recalcitrant CRS that is associated with increased disease severity and a number of surgeries [2]. Studies have revealed the inadequacy of merely aiming to reestablish sinus drainage in endoscopic sinus surgery (ESS), to treat such patients with CRS, and to postulate that the bone may serve as an alternative nidus for the infection that triggers the recurrence of the disease until it is removed [2–5]. 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%)** [2].

Evidence to date is inconclusive with regard to the etiology and pathogenesis of this bony thickening. While it has been long believed that the pathogenesis of bony changes in CRS might resemble infectious, osteomyelitis of the long bone and CRS related osteitis has been treated with prolonged culture directed oral or intravenous antibiotics [6–8]. However, these "infectious" theories lack evidence, and other theories have been recently proposed. Osteitis may simply reflect an inflammatory bone reaction caused by local bacterial infection of sinus mucosa. Histological analysis of this bony thickening describe it the process as a remodeling event and simply as

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neo-osteogenesis [9•]. For better understanding with regard to etiology and pathogenesis, various associating factors have been studied such as previous sinus surgery, severity of rhinosinusitis, inflammatory pattern of rhinosinusitis and biofilm formation. In addition, the pathogenesis of bone degradation observed in allergic fungal rhinosinusitis is to be explained.

In light of the increasing importance of bone involvement in CRS, this review aims to provide better insight into its pathogenesis, epidemiology, and correlation with clinical and biological factors.

Histological Studies

Summary of current histological studies is displayed in Table 1.

Animal Studies: Histological Data on Induced Unilateral Rhinosinusitis

Seven studies were found by the search [10–16]. Evidence of bony changes in rabbit models that were experimentally induced with unilateral rhinosinusitis was demonstrated. Pathological bony changes reported were neo-osteogenesis [10–12, 14–16], osteoclastic resorption [10–16], fibrosis [12–15], periosteal reaction [10, 15, 16], and Haversian canal changes [12, 13]. These changes observed in 92% of specimens on the infected side were similarly identified on the contralateral, non-infected side of the sinonasal complex in 52% of specimens, even in the absence of mucosal disease. This fuelled the theory that spread of disease was potentially conducted via Haversian systems to distant sites not involved in primary infection.

Several limitations to animal data exist. First, the handful of bacterial pathogens explored represent but a single etiologic component of a disease that encompasses inflammatory, environmental, host, and genetic aspects. Second, the methodology of surgical intervention during inoculation and sampling predisposes to direct infection and may therefore be the cause of the bony changes itself. Third, the short follow-up periods of these animal studies (going only up to 6 weeks post-infection) is yet another pitfall, as osteitis is noted to be a temporal sequela of the chronic disease. Finally, the experimental induction of unilateral sinusitis is a poor recreation of the human model of CRS.

Human Studies

Seven studies were found by the searches [3, 9•, 17–21]. Of seven studies studying osteitis in CRS, one study focused only on primary cases without previous sinus surgery [9•]. Most studies reported the extent of bony changes observed in

Table 1 Characteristics of histological studies

Authors, year	Study type	Participants	Number	Comparison (if any)	Outcomes
Histological animal studies					
Campos et al. [10]	Experimental	Rabbits with induced rhinosinusitis	20	None	Bone Histology
Antunes et al. [11]	Experimental	Rabbits with induced rhinosinusitis	26	Topical tobramycin versus normal saline	Bacterial count and bone histology
Khalid et al. [12]	Experimental	Rabbits with induced rhinosinusitis	29	None	Bone histology
Perloff et al. [13]	Experimental	Rabbits with induced rhinosinusitis	19	None	Bone histology
Bolger et al. [14]	Experimental	Rabbits with induced rhinosinusitis	33	None	Bone histology
Norlander et al. [15]	Experimental	Rabbits with and without induced rhinosinusitis	45	Induced rhinosinusitis versus normal	Bone histology
Westrin et al. [16]	Experimental	Rabbits with induced rhinosinusitis	21	None	Bone histology and bacteriology
Histological human studies					
Stevens et al. [17]	Cross-sectional	Patients with CRS and non-diseased	14	CRS versus non-diseased	Cellular properties of osteoblasts
Snidvongs et al. [9•]	Cross-sectional	Patients with primary CRS	22	None	Bone histology
Lee et al. [3]	Cross-sectional	Patients with CRS	121	None	Incidence rate of osteitis
Cho et al. [18]	Cross-sectional	Patients with CRS	23	None	Bone histology and radiology
Giacchi et al. [19]	Cross-sectional	Patients with CRS	20	None	Bone histology
Kennedy et al. [20]	Cross-sectional	Patients with CRS	24	None	Bone histology
Biedlingmaier et al. [21]	Cross-sectional	Patients with CRS	20	None	Bone histology and radiology

CRS chronic rhinosinusitis

accordance with neo-osteogenesis with woven bone formation, periosteal reaction, bone resorption, and fibrosis (Fig. 1). However, when only patients with primary CRS were investigated, inflammatory osteitis with inflammatory infiltration of the bone was not observed [9•]. Osteitis in primary CRS is likely a process of neo-osteogenesis and bone remodeling, rather than bone infection or inflammation.

Osteitis and Imaging

Summary of current osteitis, imaging, and assessment studies are displayed in Table 2.

Thirteen studies were found by the search [3, 18, 21–28, 29•, 30, 31]. While histopathological evaluation remains the most accurate, confirmation is feasible only where biopsy or surgery is indicated. Computed tomography (CT) presents a minimally invasive alternative and remains the most useful tool for imaging the paranasal sinuses, as it provides reliable and accurate data for mucosal hyperplasia, ostiomeatal complex (OMC) pathology, and bony changes. Osteitis is defined as rarefaction and/or irregular bony thickening of the sinus walls that exhibit signal heterogeneity together with either focal sclerosis or focal destruction (demineralization, loss of trabeculae, cortical destruction, loss of expected structures or landmarks) [21]. In term of bony thickness, Lee et al. proposed in 2006 that osteitis should be defined for each paranasal sinus (excluding the frontal sinus) when the bony wall is greater than 3 mm [3] (Fig. 2). In the same year, Kim, et al. proposed the criteria of bony wall greater than 3 standard deviations beyond the range of normal reference data (99% confidence interval). They evaluated three reference points: (1) maxillary sinus, mid-point of posterolateral bony wall in the axial section with greatest dimension of maxillary sinus; (2) ethmoid sinus, mean bony thickness of the randomly selected three bony septa in the ethmoid sinus; and (3) middle turbinate, mid-point of middle turbinate in the axial section showing the longest middle turbinate [28]. Mean bony thickness of maxillary and ethmoid sinus and middle turbinate in hyperostosis group were 3.3 mm, 2.9 mm, and 5.4 mm, respectively.

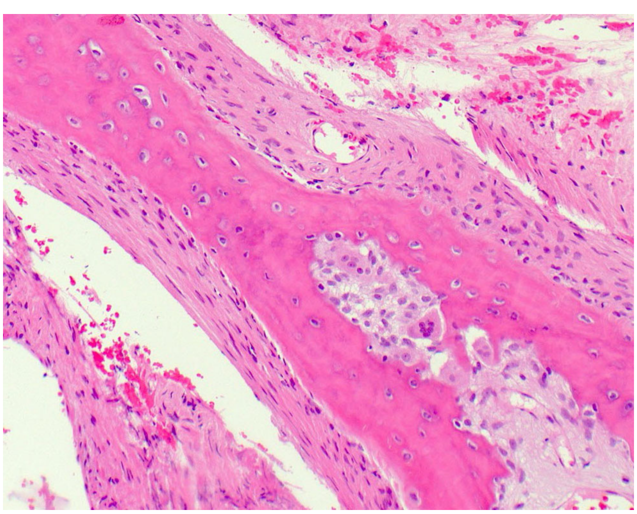

Fig. 1 Histopathology of osteitis. Osteo-neogenesis with woven bone, periosteal thickening, multinucleated osteoclasts, and fibrosis

A distinct method of CT analysis utilizing the Hounsfield unit (HU) was suggested by Cho et al. [18, 24], Emre et al. [22], Tian et al. [31], and Dong et al. [30] where osteitis was measured on a quantitative scale of radiodensity. Higher overall HU values for CRS patients were revealed with ethmoid osteitis (431.7 HU) than those without (303.2 HU) [24]. A spectrum of radiological appearance exists for osteitis in accordance with the timeline of neo-osteogenesis. Dong et al. [30] assessed bone remodeling in rabbit models by measuring the HU and found that the HU scores increased over time from 4 to 12 weeks. This team also compared the diagnostic threshold value between measuring the HU and bone thickness in rabbit models. The correlation coefficient was found greater for the HU measurement [29•]. However, it should be noted that while woven bone typically presents with a hypodensity relative to more mature stages of hyperostosis, both represent radiological thickening. Bony thickenings that qualify for radiological osteitis may therefore not yield a positive result with HU if the thickened area was mainly of woven bone [32]. In contrast with other studies, Emre et al. [22] showed less HU values of agger nasi cells for CRS patients (220.4 HU) compared with normal subjects (308.4 HU). Taking into account all factors, CT is the currently preferred modality for imaging osteitis. The role of HU is relatively recent concept, and it remains to be seen if it may have a role in future protocols for assessing osteitis.

The usefulness of radioactive imaging has also been explored in the form of single-photon emission computed tomography (SPECT) [25–27]. SPECT functions on the principle that hydroxyapatite in bone takes up varying amounts of a radioactive isotope in proportion to the rate of bone turnover, with Catalano et al. subsequently confirming the correlation of SPECT results to CT findings [23]. While a bone scan may seem the logically preferred choice, it is for the same reason of its specialized, singular purpose that it is not widely used in practice. On the other hand, CTs are routine in CRS management with or without osteitic pathology. Furthermore, radionuclear imaging comes with increased costs [32], time consumption, and need for radioactive exposure. Magnetic resonance imaging offers better resolution of soft tissue; however, this advantage is of little value in assessing bone.

Grading and Assessment of Osteitis

Five studies were found [3, 33–36]. While measuring the bony thickening has become a widely accepted form of scoring osteitis, there is currently no consensus regarding the exact degree of thickening that should represent each grade of

Table 2 Characteristics of imaging and osteitis assessment studies

Authors, year	Study type	Participants	Number	Comparison (if any)	Outcomes
Osteitis and radiograph					
Dong et al. [29•]	Experimental	Rabbits with induced rhinosinusitis	80	Diagnostic value of Hounsfield units versus bone thickness	Hounsfield units of bony paranasal sinuses
Dong et al. [30]	Experimental	Rabbits with induced rhinosinusitis	80	4 weeks versus 8 weeks versus 12 weeks after the inoculation of the bacteria	Hounsfield units of bony paranasal sinuses
Tian et al. [31]	Retrospective	Patients with CRS	250	Opaque versus non-opaque sinuses	Hounsfield units of bony paranasal sinuses
Emre et al. [22]	Cross-sectional	Patients with CRS	60	CRSsNP versus CRSwNP	Hounsfield units of bony paranasal sinuses
Cho et al. [24]	Cross-sectional	Patients with unilateral CRS	29	CRS side versus normal side	Hounsfield units of bony paranasal sinuses
Catalano et al. [23]	Cross-sectional	Patients with CRS	36	None	Correlation of SPECT with bone histology
Cho et al. [18]	Cross-sectional	Patients with CRS	23	None	Hounsfield units of bony paranasal sinuses
Lee et al. [3]	Cross-sectional	Patients with CRS	37	None	Bone histology and radiology
Kim et al. [28]	Retrospective	Patients with CRS	81	None	Association between osteitis and postoperative outcomes
Jang et al. [25]	Cross-sectional	Patients with CRS	43	CRS versus control	Quantitative isotope uptake
Nishimura et al. [26]	Cross-sectional	Patients with CRS	28	None	Correlation of bone activity to the mucosal lesions
Javer et al. [27]	Retrospective	Patients with CRS	28	None	Nuclear scan
Biedlingmaier et al. [21]	Cross-sectional	Patients with CRS	20	None	Bone histology and radiology
Grading and assessment of osteitis					
Li et al. [36]	Cross-sectional	Patients with CRS	71	None	Associations between osteitis and disease severity
Huang et al. [34]	Cross-sectional	Patients with CRS	90	None	Association between various clinical predictors and osteitis
Snidvongs et al. [35]	Cross-sectional	Patients with CRS	88	None	Associations between osteitis and histopathology, disease severity
Georgalas et al. [33]	Prospective case-control	Patients with CRS	102	None	Associations between osteitis and histopathology, disease severity
Lee et al. [3]	Cross-sectional	Patients with CRS	37	None	Bone histology and radiology

CRS chronic rhinosinusitis, *CRSsNP* chronic rhinosinusitis without polyps, *CRSwNP* chronic rhinosinusitis with polyps, *SPECT* single photon emission computed tomography

pathological change. The Kennedy Osteitis Score classified osteitis being mild (< 3 mm), moderate (4–5 mm), or severe (> 5 mm) [3, 35] Table 3. The Global Osteitis Scoring Scale added an additional component to its predecessors with the assessment of percentage sinus wall involvement and the inclusion of frontal sinus assessment [33, 34]. Li et al. [36] modified The Global Osteitis Scoring Scale by scoring only maxillary and sphenoid sinuses. Summary of osteitis grading systems is displayed in Table 4. The Kennedy Osteitis Score and The Global Osteitis Scoring Scale have been validated to show low inter-rater assessment variability, with results also correlating well with one another [33, 35]. While both scales have worked well to provide a numerical score against which osteitis may be correlated in the clinical study of associated factors, it remains to be seen if the current criteria may be further refined to more accurately reflect osteitic changes.

Many gray areas exist with regard to radiological assessment that could benefit from standardization. There is no specification with regard to the areas of sinus walls (e.g, corners, “beak” of frontal sinus floor) that should or should not qualify for “maximum thickness” [32]. This problem of variance in normal wall thicknesses also raises the question of whether ethmoid partitions should, on account of being thinner than other sinus walls, be placed on the same scale of measurement at all [32]. Furthermore, the “sharing” of common sinus walls (i.e, inter-sinus septum) in frontal and sphenoidal sinuses pose yet another dilemma [32].

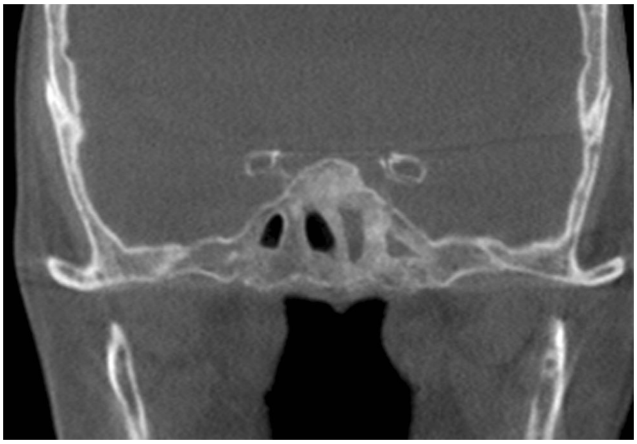

Fig. 2 CT scan image of osteitis. mm: millimeter

Osteitis and Correlative Clinical Data

Summary of current studies with regard to osteitis and correlative clinical data are displayed in Table 3.

Incidence

To assess the incidence of osteitis in patients with CRS, studies with large sample sizes ($n > 80$) were considered [2, 3, 33, 37] along with the inclusion of either radiological or histological evidence of osteitis, or both. Two studies reported the incidence by using histology [3, 37]. The different criteria employed by Lee et al. and Telmesani et al. for their histological assessment may explain the disparity of results obtained (6.7% versus 30% for primary surgery and 58% versus 87.5%, respectively), although both concur with a higher prevalence of osteitis in the revision ESS group. Three studies reported the incidence by using radiology [2, 3, 33]. Likewise, the different radiological criteria employed by Lee et al. (The Kennedy Osteitis Score) and Snidvongs et al. and Geogalas et al. (The Global Osteitis Scoring Scale) causes the disparity of results for total CRS population (36% versus 51% and 64%, respectively), primary CRS (5% versus 36.4% and 33%), and revision cases (41% versus 75.8% and 75%).

CRS Subtypes

Thirteen studies were found from the search [2, 22, 33, 34, 38–41, 42••, 43–45, 46••]. The associations of higher osteitis scores with CRSwNP [2, 22, 33, 39] and eosinophilic inflammatory pattern have been demonstrated. This was corroborated by Snidvongs et al. [2] and Mehta et al. [40] who proposed the association between osteitis and tissue eosinophilia [2]and sputum eosinophilia [40] and serum eosinophilia [2, 40] for patients undergoing both primary or revision surgeries. While tissue remodeling in patients with eosinophilic CRS has been revealed [47], the bone change observed in these patients may be caused by the process of bone remodeling. Neo-osteogenesis may be merely an endpoint of a chronic process of Th2 inflammation, driven by IL4 and IL13 [48–51]. Wang et al. assessed ethmoid bone samples from 39 patients with CRS and showed that eosinophils played an important role in the bone remodeling process in CRS with nasal polyps as eosinophils infiltrated the periosteum and induced TGF-β1 expression, periosteal thickening, increased osteoblast activity, and neo-osteogenesis [44]. Periostin production may be the other explanation as the increase in periostin expression was noted in patients with chronic rhinosinusitis with nasal polyps and in those with aspirin-exacerbated respiratory disease [43, 52]. Wu et al. [46••] assessed the mucosal sample obtained from sites of osteitic bone in patients with CRSwNP. When the bone morphogenetic protein was explored, downregulated pro-osteoblastic activity was found associated with increased osteitis. In addition, the association between osteitis and P-glycoprotein mucosal expression (which is upregulated in eosinophilic chronic rhinosinusitis) was revealed by Gunel and colleagues [42••]. When microarray analysis of the genes was assessed by this group to determine the genes which affected mucosal and bony remodeling, growth differentiation factor 5 and exostosin glycosyltransferase 1 were found upregulated and positively correlated with mucosal eosinophilic inflammation in osteitic bone [45].

Bacteria are acknowledged key elements in the pathogenesis of CRS, and they may play a role on osteitis. Huang et al. [34] found a significant association between *Pseudomonas aeruginosa* and osteitis with the odds ratio of 3.97 (95% CI 1.12–13.56) when 90 patients with refractory CRS were assessed. This association was not found with *Staphylococcus aureus*. As a disease modifier, bacterial biofilm associates with the greater expression of eosinophil major basic protein [53] and histopathologic osteitis [41] and radiologic osteitis [41]. Further studies are required to answer this unclear pathogenesis. Nevertheless, in contrast to the other studies, Zuo et al. reported their findings differently showing that the average ethmoid osteitis index in non-ECRS subgroup was significantly higher than that in ECRS subgroup [38]. There is no clear explanation for this disparity.

Revision Surgery Versus Primary Surgery

As mentioned earlier, there is a higher prevalence of osteitis in the revision ESS group [2, 3, 8, 33, 37]. Cho et al. [54] performed a dedicated study on the impact of ESS on sinus bone architecture using three groups of subjects—controls, primary patients, and revision surgery patients. The greater extent of soft tissue and bone remodeling was observed in the revision surgery group as compared with the primary and normal groups. Ethmoid bone density among the three groups was different, and patients with revision ESS had the highest bone density. Likewise, Huang et al. [34] assessed 90 patients with

Table 3 Characteristics of studies with osteitis and correlative data

Authors, year	Study type	Participants	Number	Comparison (if any)	Outcomes
Wu et al. [46••]	Cross-sectional	Patients with CRSwNP	20	CRSwNP versus healthy control	Correlation between the expression of pro-osteoblastic signaling with the degree of osteitis
Gunel et al. [45]	Cross-sectional	Patients with CRS	16	CRSsNP versus healthy control	Gene expression profiles
Huang et al. [34]	Cross-sectional	Patients with CRS	90	None	Association between various clinical predictors and osteitis
Emre et al. [22]	Prospective cohort	Patients with CRS	60	CRSwNP versus CRSsNP	Hounsfield units of bony paranasal sinuses
Wang et al. [44]	Cross-sectional	Patients with CRS	49	CRSwNP versus CRSsNP	Eosinophil infiltration of the periosteum and expression of TGF-β
Snidvongs et al. [9•]	Cross-sectional	Patients with primary CRS	22	None	Bone histology
Zuo et al. [38]	Cross-sectional	Patients with CRS	105	ECRS versus non ECRS	Osteitis, smell, histology, radiology
Dong et al. [41]	Prospective cohort	Patients with CRS	106	None	Association between osteitis and biofilms
Gunel et al. [42••]	cross-sectional	patients with CRSsNP	38	None	Association between osteitis and P-glycoprotein
Sacks et al. [55]	Prospective cohort	Patients with CRS	53	Osteitis versus without osteitis	Endoscopy, PROM
Snidvongs et al. [35]	Cross-sectional	Patients with CRS	88	None	Associations between osteitis and histopathology, disease severity
Snidvongs et al. [2]	Cross-sectional	Patients with CRS	88	None	Associations between osteitis and ECRS
Ishida et al. [43]	Prospective	Patients with CRS and AR	46	None	Pendrin and periostin expression
Bhandarkar et al. [39]	Prospective	Patients with CRS	190	Osteitis versus without osteitis	Endoscopy, olfactory, PROM
Telmesani et al. [37]	Prospective	Patients with CRSwNP	82	Primary versus revision surgery	Incidence of osteitis
Georgalas et al. [33]	Prospective case-control	Patients with CRS	102	None	Associations between osteitis and histopathology, disease severity
Cho et al. [54]	Cross-sectional	Patients with CRS	65	Primary versus revision surgery	Incidence of osteitis
Mehta et al. [40]	Cross-sectional	Patients with asthma	201	Primary versus revision surgery	Associations between osteitis and serum eosinophil, sputum eosinophil
Beule et al. [60]	Experimental	Rabbits with induced rhinosinusitis	19	Dexamethasone releasing stent versus control	Wound healing after paranasal sinus injury
Antunes et al. [11]	Experimental	Rabbits with induced rhinosinusitis	26	Topical tobramycin versus normal saline	Bacterial count and histology
Cho et al. [24]	Retrospective	Patients with unilateral CRS	29	Sinusitis side versus normal side	Hounsfield units of CT paranasal sinuses and CT score
Lee et al. [3]	Cross-sectional	Patients with CRS	121	None	Incidence rate of osteitis
Kim et al. [28]	Retrospective	Patients with primary CRS	81	None	Association between osteitis and surgical outcomes
Cho et al. [18]	Cross-sectional	Patients with CRS	23	None	Hounsfield units of bony paranasal sinuses
Richtsmeier et al. [56]	Retrospective	Patients with CRS	85	None	Causes of surgical failure

CRS chronic rhinosinusitis, *CRSsNP* chronic rhinosinusitis without polyps, *CRSwNP* chronic rhinosinusitis with polyps, *ECRS* eosinophilic chronic rhinosinusitis, *AR* allergic rhinitis, *CT* computed tomography, *PROM* patient-reported outcome measures

refractory CRS undergoing ESS and found that patients with previous sinus surgery had a greater extent of osteitis with the odds ratio of 3.5. Pathoetiologic theories suggested that surgery may open virgin bone to infection or it may leave bare bone without mucosa coverage, this may lead to reparative changes. Several pieces of bone fragments may have been left

Table 4 Characteristics of osteitis grading systems studies

Osteitis grading system	Paranasal sinuses assessed	Total score	Grading	Description
Kennedy-Osteitis Score [3, 35]	10 sinuses (right and left frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid)	0–20	Grade 0	Bony thickening < 3 mm
			Grade 1	Bony thickening 3–5 mm
			Grade 2	Bony thickening > 5 mm
Global Osteitis Scoring Scale [33]	10 sinuses (right and left frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid)	0–40	Grade 0	Less than 50% of sinus walls involved and thickening < 3 mm wide
			Grade 1	Less than 50% of sinus walls involved and thickening 3–5 mm wide
			Grade 2	Less than 50% of sinus walls involved and thickening > 5 mm wide or Greater than 50% of sinus walls involved and thickening < 3 mm wide
			Grade 3	More than 50% of sinus walls involved and thickening 3–5 mm wide
			Grade 4	More than 50% of sinus walls involved and thickening> 5 mm wide
Modified Global Osteitis Score [36]	4 sinuses (right and left maxillary and sphenoid)	0–20	Grade 1	Less than 50% of sinus walls involved and thickening 3–5 mm wide
			Grade 2	Less than 50% of sinus walls involved and thickening > 5 mm wide or Greater than 50% of sinus walls involved and thickening < 3 mm wide
			Grade 3	More than 50% of sinus walls involved and thickening 3–5 mm wide
			Grade 4	More than 50% of sinus walls involved and thickening> 5 mm wide
			Grade 5	Less than 50% of sinus walls involved and thickening 3–5 mm wide

behind and result in ongoing bone inflammation or infection. The pathogenesis of neo-osteogenesis caused by previous surgery cannot explain why patients with primary surgery experience neo-osteogenesis, and thus, the etiology of osteitis is more than a post-surgical phenomenon. To date, three studies focused their patient population on only primary CRS [9•, 28, 55]. Kim et al. and Sacks et al. assessed the impact of osteitis on prognosis which will be later discussed [28, 55]. Snidvongs et al. studied histopathology of neo-osteogenesis of primary CRS and reported no evidence of inflammatory infiltrate of bone in any bone samples [9•]. New woven bone formation and osteoblastic activity were the key histopathologic characteristics of this bone change. Taking these findings for consideration together with the association between neo-osteogenesis and nasal polyps and eosinophilic inflammation, this non-inflammatory reactive bone change in primary CRS may be one feature of bone remodeling found in eosinophilic subgroup (eCRS). Periostin, mentioned previously, is also a feature of the eCRS subtype [52]. Further studies are required to answer this unclear pathogenesis.

Symptom Severity

Despite strong evidence for the positive correlation of osteitis with worse disease severity, it is interesting to note that this association is not mirrored when correlated with clinical severity. Studies which have contributed to this finding have employed a wide range of validated instruments such as the Visual Analogue Scale (VAS) [33], the Rhinosinusitis Disability Index (RSDI) [33, 39], the Chronic Sinusitis Survey (CSS) [39], the nasal component of the Rhinosinusitis Outcome Measure (RSOM-31) [33], and the Sino-Nasal Outcomes Test (SNOT-22) [2]. These patient-reported outcome measures failed to report a worse baseline quality of life score in patients with osteitis when compared with non-osteitis patients.

Lund-MacKay Scores

There has been strong evidence for the positive correlation of osteitic changes to the severity of CRS. Using Biedlingmaier's criteria for bone grading [21], Cho et al. found patients with a higher bone grades to a have higher Lund-MacKay scores, as well as increased bone density on CT when measured by HU [18]. In the study by Lee et al., the average Lund-MacKay score for patients with CRS and osteitis was 22 compared with just 6.5 for non-osteitic patients [3]. The broad prospective studies conducted by Huang et al. [34], Georgalas et al. [33], Cho et al. [24], Kim et al. [28], and Snidvongs et al. [2] once again reaffirmed the statistically significant association of higher osteitic scores with greater severity of disease.

Osteitis and Relevance for Prognosis

Osteitis has been proposed as a prognostic factor for poor post-operative outcome in a study by Richtsmeier et al. [56], Bahandakar et al. [39] and Kim et al. [28] who noted a significant association between hyperostosis and poorer postsurgical outcomes. It should be noted that this association may also be attributed to the higher Lund-MacKay scores of the patients in this particular subject group. It remains unknown if surgical intervention and the outcome of osteitis represent a cause-effect relationship or merely share a common endpoint of recalcitrant disease requiring persistent treatment. In contrast to other studies, Sacks et al. conducted a prospective a cohort study of 53 patients with CRS and reported no association between the presence or severity of osteitis at the time of surgery and clinical outcomes at 1-year post-primary ESS. However, the presence of osteitis was associated with the need for a course of oral steroid post-surgery, and this may be reflective of the patients' eosinophilic subtype [55].

Specific Treatments of CRS with Osteitis

Data regarding specific treatment of CRS patients with osteitis remains wholly scarce. A couple of studies have pushed for the advent of radical surgery to remove all involved bone, on the premise that better clinical outcomes may be obtained if bone is eradicated as the source of persistent inflammation [3, 4, 7, 33, 57]. While this appears a logical conclusion, a recent study has in fact revealed worse outcomes following radical surgery for patients with osteitis [39]. It should not be forgotten that surgery has been correlated with worse severity of disease, even if just by secondary association and that the decision for radical surgery should be undertaken with caution [58].

Long-term, high-dose antibiotic therapy analogous to the treatment of osteomyelitis, has no basis in our current understanding of the disease process that produces osteitis or neo-osteogenesis in CRS patients. No study to date has identified bacteria within bone specimens that correlate to the presence of osteitis. Macrolide antibiotics, with their dual anti-inflammatory and antibacterial properties, offered an attractive solution to this dilemma [5] until recent evidence proved the contrary. Snidvongs et al. advocated an intensive post-operative corticosteroid therapy regime for patients with high eosinophilia to target systemic mediators, such as periostin [2]. Other studies in this direction have begun testing the efficacy of topical steroids in animal models [11] as well as designing novel drug delivery systems to overcome the problem of poor bone penetration [59].

Conclusions

There is an increasing evidence for the association of CRS severity with osteitic changes within the underlying bone of paranasal sinuses, where a higher prevalence of bony remodeling has been reported in patients with higher Lund-Mackay scores or increased incidence of revision surgeries. While CT has become a staple in osteitis assessment, the standards for grading osteitic severity are undergoing further research, but 3 mm remains a good current threshold. More importantly, the findings of osteitis in more than a third of CRS patients with no prior history of surgery suggest osteitis may be a reparative neo-osteogenesis rather than a true inflammatory process No data exists to suggest that the observed bone changes are infective in nature. A number of studies have attempted to establish a link between osteitis and clinical severity, however, there seems to be no significant association of bone involvement to symptom scores or impact on quality of life. Recent studies suggest that osteitis is a marker of the eosinophilic subtype of CRS with nasal polyps and may result from local or systemic mediators of inflammation such as periostin.

Compliance with Ethical Standards

Conflict of Interest Kornkiat Snidvongs has served speakers' bureau for the Merck Sharp Dolme and Menarini. Raymond Sacks is a consultant for the Medtronic and Olympus and speakers' bureau for Seqiris Pharmaceutical. Richard J Harvey is a consultant with the Medtronic, Olympus, and NeilMed pharmaceuticals; he has been on the speakers' bureau for the GlaxoSmithKlin, Seqiris, and Astra Zeneca.

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• Of importance
•• Of major importance

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