

# Role of Osteitis in Chronic Rhinosinusitis: A Predictive Marker of Disease Severity?

<https://doi.org/10.47210/bjohns.2021.v29i2.431>

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## ABSTRACT

### Introduction

Chronic rhinosinusitis (CRS) not only affects the overlying mucosa but also involve the underlying sinus bone termed as osteitis. The role of osteitic bone in severity and persistence of disease has received little attention. Thus understanding of this can help in formulating better treatment plan for CRS. We conceived this study with an aim to assess correlation of osteitis with severity of disease and short term disease outcome by examining the various parameters concerned with CRS.

### Materials and Methods

This prospective cohort study included 40 participants as clinically diagnosed CRS cases and 20 participants as controls. Various pre and post-operative parameters concerning CRS were assessed like pre and post-operative Sino-Nasal Outcome Test (SNOT) 20 symptom score, Lund-Kennedy endoscopy and Lund Mackay CT scores, bone density / Hounsfield unit (HU), radiological bone thickness and histopathological mucosal and bone grading. Correlation between osteitis and all these parameters were analyzed.

### Results

Osteitis / bone grade was found to have statistically significant, moderate and positive correlation with the preoperative Lund and Mackay CT score and mucosal grade. The osteitis / bone grade was found to be weakly and positively correlated to the Lund and Kennedy score and weakly but negatively correlated to change in SNOT- 20 values (both statistically insignificant).

### Conclusion

There are high chances of harbouring severe osteitis underneath high grade mucosal disease in CRS. Preoperative Lund and Mackay CT score can serve as a surrogate marker for osteitis. Symptomatic severity of disease does not correlate with osteitis. Osteitis affects disease outcome negatively.

### Keywords

Sinusitis; Osteitis; Endoscopy; Tomography, X-Ray Computed; Sino-Nasal Outcome Test

Chronic rhinosinusitis (CRS) can be defined broadly as a chronic (> 12 weeks duration) inflammatory condition of nose and paranasal sinus mucosa, underlying bone or both and can also have fluid inside the sinus cavities, and it should be appreciated irrespective of treatment status.<sup>1</sup> There have been infrequent amendments in the defined diagnostic criteria for CRS and the most updated and widely followed are the recent recommendations for CRS by American Academy of Otolaryngology - Head and Neck Surgery (AAO-HNS). The AAO-HNS suggests including both subjective and objective parameters of more than 12 weeks duration. The subjective component considers 2 or more of the 4 main symptoms (anterior and/ or posterior mucopurulent discharge, nasal stuffiness, pressure-fullness-pain in face & hyposmia) and the objective includes inflammation

which was characterized by one or more of these (purulent character of mucus / edema present in middle

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meatus or the ethmoid area, NPs (nasal polyps) or the polyps in middle meatus; and/or, radiological imaging showing inflamed paranasal sinuses).<sup>2,3,4</sup> To evaluate the objective components of CRS diagnosis, Diagnostic Nasal Endoscopy (DNE) and Computed Tomography (CT) scan play important role.

CRS is not only limited to the overlying mucosa but also involve the underlying sinus bone. Analysis of ostiomeatal unit (OMU) CT scans and pathological slides had focused on soft tissues including mucosa, but changes in the underlying bone have frequently been overlooked. Bone involvement in CRS has been variously termed as osteitis/osteomyelitis/hyperostosis/bone hyperplasia and neo-osteogenesis. As there is no marrow in flat bones around the sinuses, the term osteitis is recommended.<sup>5</sup> CT scans in patients of CRS often reveal areas of increased bone density and irregular thickening of sinus walls. Also, some studies have shown radiological and histopathological evidence of bone involvement in chronic rhinosinusitis.<sup>6,7</sup> Still, the role of osteitic bone in severity and persistence of disease has received little attention. Therefore, for formulating better treatment plan in CRS, understanding the magnitude of bone involvement and relationship between the mucosal and bony changes (radiological and histopathological) are important. Thus, we conceived this study with an aim to assess correlation of osteitis with severity of disease and short term disease outcome by examining the various parameters concerned with CRS (radiological staging, endoscopic staging, pre-operative SNOT 20 scoring and symptom scores). We also had an objective to observe correlation between the various other parameters, with respect to each other.

## Materials and Methods

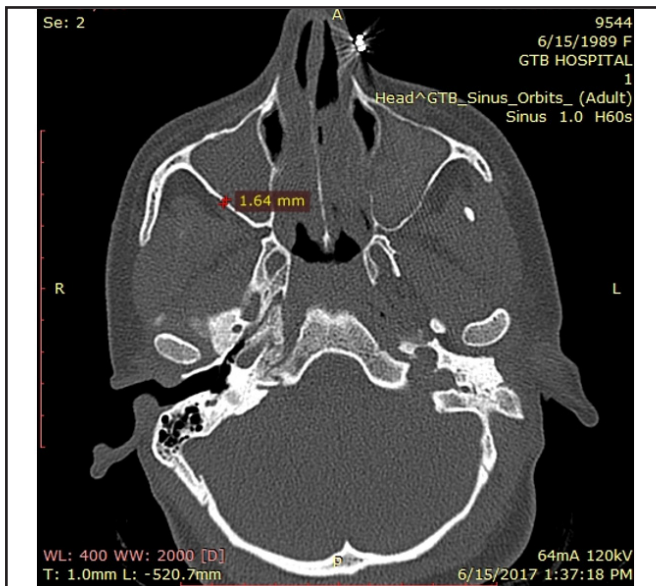
The prospective cohort study was conducted in Department of Otorhinolaryngology in collaboration with Department of Pathology and Department of Radiology at a tertiary care Hospital over a period of 18 months.

Forty (40) participants were included as clinically diagnosed CRS cases and 20 participants as controls (Patients undergoing nasal surgery for non-inflammatory causes such as septoplasty or septorhinoplasty).

Patients having CRS with bronchial asthma, immunocompromised status, pregnancy, mucociliary dysfunction (cystic fibrosis), sinonasal malignancies, prior nasal surgery, sinonasal trauma, post radiotherapy status to head and neck and secondary causes of CRS were excluded from this study.

Informed and written consent was taken from all participants. Detailed History using standard Visual Analogue Scale of SNOT-20 questionnaire was documented for all. Routine otorhinolaryngological examination (including anterior and posterior rhinoscopy, ear and oral cavity) was done. The participants were then subjected to Diagnostic nasal endoscopy (DNE) and CT paranasal sinuses- (to obtain images in axial, coronal and sagittal views). The findings obtained were scored with the help of standard Lund-Kennedy endoscopy system and Lund Mackay CT scoring system.<sup>8,9</sup> The Hounsfield unit (HU) was measured at bulla ethmoidalis in the CT sections through the osteomeatal unit, as an indirect indicator for the bone density.<sup>10</sup> We also evaluated bone thickness for all participants by CT scan. Bone thickness was evaluated for the maxillary sinus- at the midpoint of the posterolateral bony wall (in the axial section at the greatest dimension of the maxillary sinus) (Fig. 1), for ethmoid sinus- by including the mean bony thickness of three randomly selected bone septa (Fig. 2) and for middle turbinate, at the midpoint of the it, in the axial section (Fig. 3).<sup>11</sup> The measurements were performed 3 times randomly and the mean and standard deviation were calculated.

Cases underwent Functional endoscopic sinus surgery. Bone and mucosa were harvested from operative site in cases and in controls. Mostly the ethmoid septa were collected as bone samples in cases and part of bony septum in controls. The Biopsy samples were preserved in 10% buffered formalin for Histopathological examination (HPE). The biopsy specimen was routinely processed, paraffin embedded and Hematoxylin and Eosin stained slides were prepared & examined. In order to get an objective score of disease severity, the osteitis & mucosal grading was scored using predefined criteria.<sup>12</sup> Various osteitis grades are as follow; Grade 0 (for normal bone), Grade 1 (for periosteal thickening), Grade 2 (Grade 1 + osteoblastic and osteoclastic activity with bone resorption and/or remodeling), Grade 3 (Grade

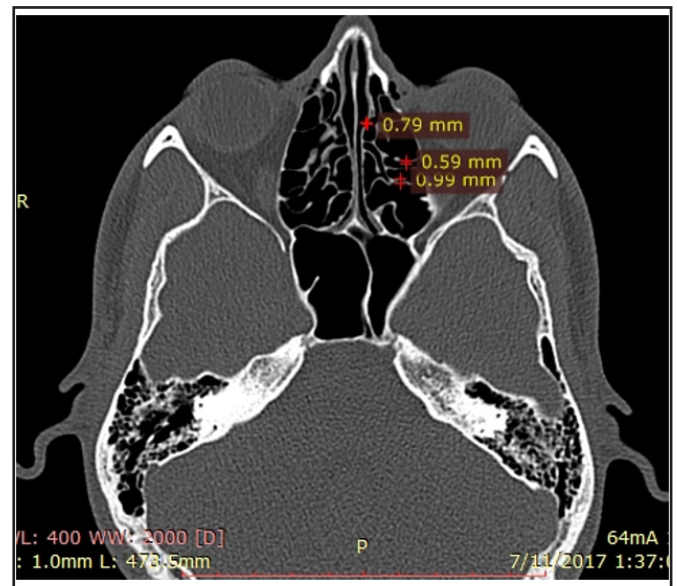


**Fig.1.** Bone thickness for the maxillary sinus, at the midpoint of the posterolateral bony wall, in the axial section at the greatest dimension of the maxillary sinus.

2 + wide osteoid matrix), Grade 4 (frank osteomyelitis, leucocytes infiltration and bone destruction). The pathologist was blinded to the symptom severity and CT scores. Data also collected regarding outcome measures



**Fig.3.** Bone thickness for the middle turbinate, at the midpoint of the middle turbinate, in the axial section with longest middle turbinate.



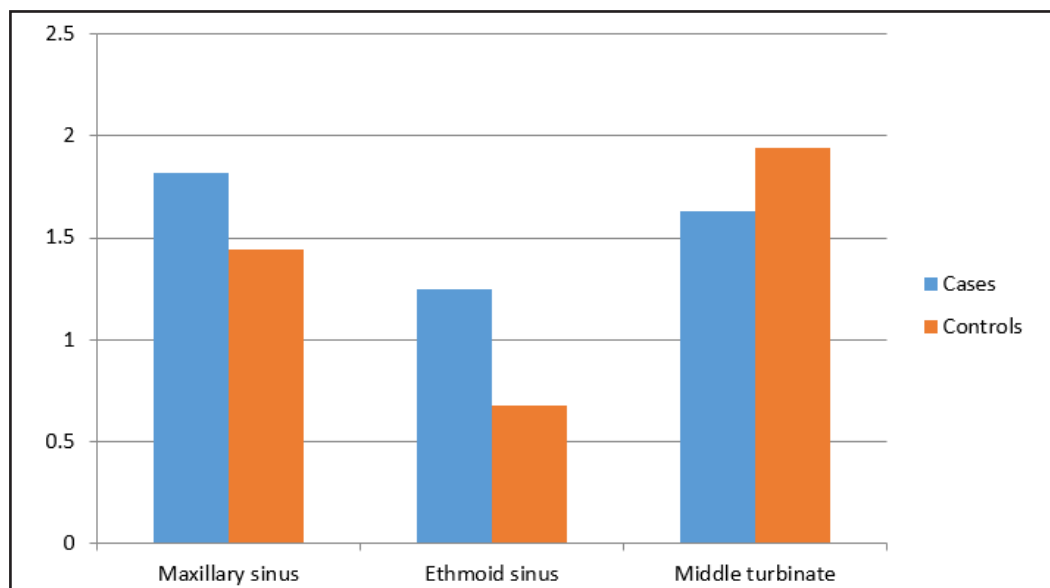
**Fig.2.** Bone thickness for the ethmoid sinus, including the mean bony thickness of three randomly selected bone septa.

using SNOT-20 and DNE in the follow up period after 3 months postoperatively.

*Statistical analysis:* Pearson correlation was applied to find correlation between various parameters including symptoms score, Lund-Kennedy endoscopy scores and Lund Mackay CT score, bone density (HU scores), osteitis score and mucosal grading. Unpaired student t-test and Mann-Whitney test were used based on their applicability to compare the parameters. SPSS version 23 statistical software was used to analyze the data.

## Results

The median age at the time of presentation in the case group was 24 years with range of 18-61 years while in the control group was 22.5 with the range of 18-58 years. The study included 22 males and 18 females in the case group while 16 males and 4 females in the control group. The disease was found to be unilateral in 15 cases and Bilateral in 25 cases. Nasal obstruction was present in all the 40 patients i.e. 100% cases. The mean SNOT-20 score improved from 22.85 (Preoperative) to 5.92 (Postoperative). (Table I) Mean endoscopic score (Mean  $\pm$  SD) of CRS patients



**Fig.4. Comparison of mean bone thickness of maxillary sinus, ethmoid sinus and middle turbinate (in mm) between cases and controls.**

improved from  $5.02 \pm 1.50$  preoperative to  $3.17 \pm 0.38$  postoperatively. The mean preoperative CT score according to Lund and Mackay staging system was  $13.51 \pm 2.57$  (Mean  $\pm$  SD). Anterior Ethmoids were involved (partial or complete opacification) in 38 (95%) patients and Posterior Ethmoids were involved in 35 (87.5%) patients. Maxillary sinus and Osteomeatal complexes were blocked in 40(100%) cases. Sphenoid sinus was involved in 28 cases, i.e. 70% and Frontal sinus in 28 cases, i.e. 70% cases. (Table II). The mean HU in patients of CRS was  $350.525 \pm 94.74$  which was significantly different from controls group which was  $270.950 \pm 58.43$  ( $p=0.001$ ).

The mean bone thickness (Mean  $\pm$  SD) for maxillary sinus in patients of CRS was  $1.819 \pm 0.72$  which was significantly different from controls group  $1.439 \pm 0.49$  ( $p=0.038$ ). The mean Bone thickness for ethmoid sinus in cases was  $1.251 \pm 0.515$  which was significantly different from controls group which was  $0.678 \pm 0.187$  ( $p= 0.001$ ). (Fig. 4)

The mean bone thickness for middle turbinate in cases was  $1.628 \pm 0.474$  which was significantly different from controls group  $1.944 \pm 0.735$ . ( $p=0.049$ ) [Showing a higher value in controls]. This might be because of resorption of middle turbinate by the disease in CRS

patients. Also, it was observed that middle turbinate was not well visualized in its whole length in cases of CRS with polyps. Histopathological examination in 40 cases showed; Normal bone in none, Grade 1 osteitis in 10 cases (25%), Grade 2 osteitis in 20 cases (50%), Grade 3 osteitis in 10 cases (25 %) and Grade 4 in none. Histopathological examination in 20 controls showed; Normal bone in 18 cases (90 %), Grade 1 osteitis in 2 cases (10 %), Grade 2 osteitis in 0 cases, Grade 3 osteitis in 0 cases and Grade 4 in 0 cases. The median value of Bone grade in cases was 2 while in the control group was 0. The difference in values was statistically significant ( $p=0.001$ ). Mucosal grades in 40 cases were as follows; Grade 0 (normal) in none, Grade 1 in 1 case (2.5%), Grade 2 in 9 cases (22.5%), Grade 3 in 26 cases (65%) and Grade 4 in 4 cases (10%). Mucosal grades in 20 controls were as follows; Grade 0 (normal) in 17 cases (85 %), Grade 1 in 3 cases (15 %), Grade 2 in 0 cases, Grade 3 in 0 cases and Grade 4 in 0 cases. The median value of mucosal grade in 40 cases was 3 while in the control group it was 0. The difference in the values was statistically significant ( $p=0.001$ ).

**Correlations:** Pearson correlation coefficient was used to correlate the various parameters.

The osteitis/bone grade was found to be weakly



**Table I: Preoperative and Postoperative SNOT-20 score in cases.**

SNOT-20 SCORE	PRE-TREATMENT (NO. OF PATIENTS)	POST TREATMENT (NO. OF PATIENTS)
0-10	2	32
11-20	18	7
21-30	16	1
31-40	4	0
41-50	0	0

and positively correlated to the Lund and Kennedy score ( $r=0.294$ ) but the correlation was not significant ( $p=0.065$ ). The osteitis/bone grade was found to be moderately and positively correlated to the preoperative Lund and Mackay CT score ( $r=0.406$ ,  $p=0.009$ ). This correlation was found to be statistically significant, and higher osteitis score was thus associated with higher CT scan staging. The Bone grading/Osteitis score was found to be moderately and positively correlated to the mucosal grade. This correlation was also found to be significant ( $r=0.338$ ,  $p=0.033$ ). The Osteitis score was also found to be weakly but negatively correlated to change in SNOT- 20 values ( $r=-0.255$ ), but the correlation was found not to be statistically significant ( $p=0.112$ ). The Bone grading was not found significantly correlated to any other parameter.

Preoperative SNOT-20 values were found to be moderately and positively correlated to the bone density / HU ( $r=0.407$ ,  $p=0.009$ ) and bone thickness at Ethmoid sinus ( $r=0.434$ ,  $p=0.005$ ). This correlation was found to be significant, indicating that higher symptom score is associated with higher bone density and higher bone thickness at the Ethmoid sinus. Preoperative SNOT-20 values were found to be fairly and positively correlated to the Lund and Kennedy score. But this correlation was not found to be significant ( $r=0.299$ ,  $p=0.061$ ). Pre-operative SNOT-20 values were not found to be significantly correlated to any other parameter.

The Lund and Kennedy scoring based on the pre-

**Table II: Percentage of sinus involvement**

SINUSES INVOLVED	NUMBER OF PATIENTS	PERCENTAGE
Anterior Ethmoids	38	95%
Posterior Ethmoids	35	87.50%
Maxillary	40	100%
Sphenoid	28	70%
Frontal	28	70%
Osteomeatal complex	40	100%

operative DNE was found moderately and positively correlated to the mucosal grade ( $r=0.459$ ,  $p=0.003$ ) & symptom score (measured as the difference between preoperative and postoperative SNOT-20 values) ( $r=0.362$ ,  $p=0.022$ ) but moderately and negatively correlated to the bone thickness of the maxillary sinus (BTMS) ( $r= -0.340$ ,  $p= 0.032$ ), these correlations were found to be statistically significant (the attribute to this may be pressure erosion of the bone due to more severe symptomatic mucosal disease). Besides, as mentioned with osteitis & preoperative SNOT 20 score, no other parameter was found to have statistically significant correlation with it.

Besides osteitis, the preoperative Lund and Mackay CT score was also found to be moderately and positively correlated to the mucosal grade ( $r=0.386$ ,  $p=0.014$ ). This correlation was found to be statistically significant. Higher CT scan staging was thus associated with higher mucosal disease. Lund and Mackay score was not found significantly correlated to any other parameter.

Mucosal grade had statistically significant (good and positive) correlation with the duration of disease ( $r=0.688$ ,  $p=0.001$ ). The mucosal grading was not found to be significantly correlated to any other parameter except the aforementioned correlations.

The duration of disease had statistically significant (good and positive) correlation with bone thickness at the ethmoid sinus ( $r=0.709$ ,  $p=0.001$ ). The duration of disease was found to be weakly and positively correlated

to the bone thickness of the maxillary sinus but this correlation was not statistically significant ( $r=0.278$ ,  $p=0.082$ ). The duration of disease was not found to be correlated to any other parameter except as mentioned with mucosal grade above.

Other than the correlations mentioned above, improvement in clinical symptoms (measured as the difference between preoperative and postoperative SNOT-20 values) was found moderately and positively correlated to the bone density/HU score ( $r=0.32$ ,  $p=0.043$ ) and bone thickness of the Ethmoid sinus ( $r=0.366$ ,  $p=0.020$ ), both these correlations were found to be statistically significant. No other parameters were found having statistically significant relation with symptom score.

## Discussion

Osteitis can be defined as increased simultaneous osteoblastic and osteoclastic activity in varying proportion whereby resulting in disruption of organized lamellar bone and immature woven bone formation.<sup>13</sup> With respect to CRS, the osteitic changes were described in ethmoid bone which included inflammatory infiltrate, neo-osteogenesis, bone remodeling and sclerosis.<sup>14</sup> Although very few in number when compared with its mucosal counterpart, but there have been studies showing radiological and histopathological evidence of bone involvement in chronic rhinosinusitis.<sup>6,7</sup> Thus addressing the underlying osteitis in CRS patient, has been suggested as a mandatory therapeutic choice to attain long lasting results.<sup>15</sup> This could have implications in the recurrence of mucosal disease after surgical treatment and may indicate that these osteitic lesions act as a source of chronic inflammation.<sup>6,14,16</sup> Although there are two main defining criteria for osteitis including radiological and histopathological. Since osteitis is a pathological phenomenon we chose histopathological definition for our study as described by Biedlingmaier et al.<sup>12</sup>

In the study population, Cases and Controls showed significant difference in grading for osteitis and mucosal inflammation. The difference in the values between cases and controls were found to be statistically significant. In our study we found that the mucosal

disease was higher in the grade of inflammation than the osteitis in CRS patients. These results are comparable to study conducted by Eugene Mutijama et al.<sup>17</sup> The osteitis score in our study was found to have statistically significant moderate and positive correlation with the mucosal grade in contrast to the study mentioned above, suggesting that there are high chances of having severe osteitis in CRS patients who has high grade mucosal disease.

We also found statistically insignificant but a weak and positive correlation of osteitis with the Lund and Kennedy score. The osteitis was found to be moderately and positively correlated to preoperative Lund and Mackay CT score (statistically significant), indicating that the higher osteitis score was thus associated with higher CT scan staging. These results were found comparable with other studies where osteitis defining criteria were radiological.<sup>18,19</sup> It was proposed by this study that patients having osteitis may benefit from post-operative corticosteroid therapy to prevent recurring osteitis.<sup>18</sup>

We did not find any significant correlation between osteitis and pre-operative SNOT 20 score, however a statistically non-significant, weak but negative correlation was found with change in SNOT- 20 values ( $r = - 0.255$ ,  $p = 0.112$ ). In contrary to the implicit assumption that the disease severity in terms of symptomatology would be seen more in severe osteitis, we find no such correlation between the two. Although we do not have any strong evidences to support but we propose that the indolent nature of the underlying chronic osteitis can be held responsible for less symptom severity as in comparison to the symptom severity of acute rhinosinusitis. These results also correlate with results of study conducted by Georgalas et al.<sup>19</sup> However defining disease outcome based on SNOT 20 scores, even with weak correlation, this can still be understood that the osteitis affects the CRS outcome adversely. Bhandarkar et al. while assessing the impact of osteitis in disease severity and quality of life outcomes in CRS, concluded that osteitis is associated with worse baseline measures of disease severity and the presence of osteitis is associated with a reduced chance of improvement in CRS.<sup>20</sup> We found no significant correlation between osteitis and duration of disease.

*Other important inferences:* Preoperative SNOT-20 values were found to be moderately and positively correlated to the bone density/HU and bone thickness at Ethmoid sinus. This correlation was found to be significant, indicating that higher symptom score is associated with higher bone density and higher bone thickness at the Ethmoid sinus. The duration of disease had statistically significant (good and positive) correlation with bone thickness at the ethmoid sinus. Improvement in clinical symptoms (measured as the difference between preoperative and postoperative SNOT-20 values) was found moderately and positively correlated to the bone density/HU score ( $r=0.32$ ,  $p=0.043$ ) and bone thickness of the Ethmoid sinus ( $r=0.366$ ,  $p=0.020$ ), both these correlations were found to be statistically significant.

## Conclusion

This study found that, osteitis has a significant correlation with histopathological mucosal grade and thus there are high chances of harbouring severe osteitis underneath the high grade mucosal disease in CRS. Preoperative Lund and Mackay CT score can also serve as a surrogate marker for osteitis as the two shows moderate and positive correlation. Preoperative Lund and Kennedy endoscopy score are not significantly useful in this direction. Contrary to the usual presumption, symptomatic severity of disease does not correlate with osteitis severity as it appears so, may be because of the indolent course of osteitis. However, a statistically non-significant, weak but negative correlation exists between osteitis and disease outcome. This suggests a role of assessing osteitis in CRS to predict outcome, as the severe underlying osteitis will serve as a proxy indicator of recurrence/adverse outcome. Even though we conclude several important facts from this study, at the same time we would acknowledge that this study was conducted with limited number of participants hence studies including larger study populations are needed to testify the facts.

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