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ORIGINAL RESEARCH

Correlation of Eosinophils and Type 2 Inflammatory Mediators with Osteitis in Chronic Rhinosinusitis with Nasal Polyps

Zhidi Zhang, Qiang Zuo, Yali Du, Hailing Jiang, Furong Ma, Yinghong Zhang

Department, Otolaryngology Head and Neck Surgery, Peking University Third Hospital, Beijing, 100191, People's Republic of China

Correspondence: Yinghong Zhang, Department, Otolaryngology Head and Neck Surgery, Peking University Third Hospital, Beijing, 100191, People's Republic of China, Email yinghongzhang@bjmu.edu.cn; Furong Ma, Department, Otolaryngology Head and Neck Surgery, Peking University Third Hospital, Beijing, 100191, People's Republic of China, Email furongma@126.com

Objective: Osteitis is more prevalent in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), making the disease refractory and prone to recurrence. However, the pathophysiologic mechanism of osteitis formation in CRS has not been fully elucidated, and this study aimed to further elucidate the association of eosinophils and type 2 inflammatory mediators with osteitis in patients with CRSwNP.

Methods: This retrospective study collected clinical data on 125 cases of CRSwNP. The participants were categorized into two groups based on the presence or absence of osteitis in their sinus CT scan. The groups were classified as the osteitis group and the non-osteitis group. The clinical baseline data, type 2 inflammatory mediators, and eosinophils were compared between the two groups. The correlation between these factors and the Global Osteitis score scale (GOSS) was also evaluated.

Results: There were 69 cases in the osteitis group and 56 cases in the non-osteitis group of CRSwNP patients. The prevalence of concomitant asthma (P=0.009), SNOT-22 score, LUND-MAKAY score, and LUND-KEDENY score were significantly higher in the osteitis group than in the non-osteitis group (All P values were < 0.001); the absolute values of IL-13 (P<0.001), periosteal proteins (P<0.001), and tissue eosinophils (P < 0.05) were significantly higher in the osteitis group as compared with the non-osteitis group. Logistic regression analysis showed that IL-13 and periosteal proteins were risk factors for CRSwNP osteitis (P<0.001). ROC curve analysis revealed that IL-13 had the highest predictive value (AUC=0.786) with a cut-off value of 5.8059 pg/mL, the sensitivity of 58.0%, and a specificity of 89.3% respectively.

Conclusion: Osteitis could indicate the more severe symptoms of chronic rhinosinusitis with nasal polyps (CRSwNP), and elevated IL-13, periosteal proteins, and tissue eosinophils are risk factors for osteitis formation in patients with CRSwNP.

Keywords: chronic rhinosinusitis, osteitis, eosinophils, type 2 inflammatory mediators

Introduction

Chronic rhinosinusitis (CRS) is a multifactorial, highly heterogeneous, long-term inflammatory disease of the nasal cavity and sinuses, which greatly affects the quality of life of patients. The prevalence of CRS ranges from 5–12%, with up to 8% of the population in China suffering from this disease[1,2]. Patients with CRS can greatly improve their quality of life with systematic drug and surgical treatments, but there are still some patients with recurrent or even further deterioration of symptoms after long-term standard treatments, known as refractory chronic rhinosinusitis (RCRS)[3]. Sinus lesions in RCRS not only involve the mucosa but also the bone, and the hyperplasia, sclerosis, and inflammation of the bone in turn aggravate the persistence of the inflammatory state, leading to prolonged illness in patients with CRS.[4] Osteitis in CRS has been defined as a process of new bone formation and bone remodeling in the sinuses, which is mainly characterized by periosteal thickening and new woven bone formation[5]. Osteitis was found to occur in 51% of patients with CRS, and the incidence was even higher in 76% of patients who had undergone previous sinus surgery,

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thus, osteitis is considered to be an important cause of disease progression and high recurrence rate in refractory sinusitis[6].

The concept of inflammatory endotypes has gradually gained importance in CRS in recent years, with inflammatory endotypes referring to different complex inflammatory states in the nasal sinuses. In the EPOS 2020 guidelines, it was proposed to categorize CRS into type 2 CRS and non-type 2 CRS based on inflammatory endotypes, where type 2 inflammation is considered to be strongly associated with polyp formation and recurrence in patients with chronic rhinosinusitis with polyps (CRSwNP).[7] Previous studies by our group have found that eosinophils and type 2 inflammatory mediators play an important role in symptoms of olfactory impairment in patients with chronic sinusitis.[8] Although the occurrence of osteitis suggests the severity and refractory nature of the disease, the exact causal relationship between osteitis and the inflammatory endotype of CRS remains unclear. This study aimed to investigate the relationship between type 2 inflammatory mediators and eosinophils and osteitis in patients with CRS and to further identify and analyze the risk factors for the formation of osteitis.

Methods

Subjects and Study Design

The design of this study was to review 125 patients with CRSwNP who were hospitalized at Peking University Third Hospital and underwent functional nasal endoscopic sinus surgery from January 2022 to January 2024 when they attended the hospital. The study was approved by the Ethics Committee of the hospital (Ethics Committee Approval No. 005–01). Written consent was obtained from each patient. The diagnosis of CRSwNP was made according to the European Position Paper on Sinusitis and Nasal Polyps (EPOS 2012).[7] Exclusion criteria: exclude diseases such as fungal sinusitis, inverted papilloma, abnormal proliferation of bone fibers, and ossifying fibroma. General clinical information about the patient was collected, including age, sex, disease duration, smoking history, history of previous sinus surgery, and concomitant symptoms (asthma, allergic rhinitis, aspirin intolerance triad). The diagnosis of asthma was determined by a single pulmonologist, and the diagnosis of aspirin intolerance triad and allergic rhinitis was based on a detailed clinical history. The subjective symptoms of CRSwNP patients were scored using the SNOT-22 rating scale,[9] which is divided into 22 symptomatic entries, each of which is scored from 0 to 5 from mild to severe, with a score of 0 indicating an impact and 5 indicating a very high impact, and finally the total score was calculated by the physician. Nasal endoscopy was assessed for severity based on the Lund-Kennedy scoring system,[10] which included polyps (0=no polyps, 1=polyps only in the middle nasal passage, 2=polyps beyond the middle nasal passage), edema (0=none, 1=mild, 2=severe), leakage (0=none, 1=clear, thin leakage, 2=mucoid, purulent leakage), scarring (0=none, 1=slight, 2=severe), and crusts (0=none, 1=mild, 2=severe), with a score of 0–10 points on each side, for a total score of 0–20.

Eosinophils and Type 2 Inflammatory Mediators

Preoperative blood samples were collected from patients for testing the absolute serum eosinophil values, all done by the biochemical laboratory of the Department of Laboratory Medicine, Peking University Third Hospital. Nasal polyp tissues were obtained during functional nasal endoscopic surgery and analyzed by hematoxylin-eosin staining, and 5 high magnification fields of view (HPF, × 400) were randomly selected in the sections, and the average value was taken to calculate the number of eosinophils. The nasal secretions of patients were collected, and gelatin sponges were placed into the middle nasal passage for 5 minutes, removed, diluted with 0.9% saline, centrifuged, and the supernatant was obtained, and the double-antibody one-step sandwich enzyme-linked immunosorbent assay (ELISA) (Dogesce, China) was performed with the human IL-4, IL-5, IL-13, and periostin quantitative enzyme-linked immunoassay kits. The concentration of the samples was calculated according to the instructions of the reagents.

Imaging CT and Osteitis GOSS Score

All patients underwent sinus CT scan before operation to evaluate the presence of bone hyperplasia. The severity of sinusitis were scored using the Lund-Mackay scoring system,[11] which scored the maxillary sinus, anterior group of sieve sinuses, anterior group of ethmoid sinus, posterior group of ethmoid sinus, sphenoid sinus, frontal sinus, and ostiomeatal complex, in that order. Scoring criteria: (1) sinuses: 0 points = no abnormality, 1 point = partial turbidity, 2 points = total

turbidity; (2) ostiomeatal complex: 0 points = no obstruction, 2 points = obstruction; (3) 0 to 12 points for each side, with a total score of 0 to 24 points.

The severity of osteitis was measured using the Global Osteitis score scale (GOSS),[12] with 1 being sinus wall osteitis ranging from ≤50% and osteitis thickness <3 mm; 2 being sinus wall osteitis ranging from ≤50% and osteitis thickness 3–5 mm; 3 being sinus wall osteitis ranging from ≤50% and osteitis thickness >5 mm, or sinus wall osteitis ranging from >50% and osteitis thickness <3 mm; 4 being sinus wall osteitis range >50%, osteitis thickness 3–5 mm; 5 is sinus wall osteitis range >50%, osteitis thickness >5 mm. Scores for each sinus ranged from 0–5, and scores for all sinuses (bilateral frontal sinuses, anterior group of ethmoid sinus, posterior group of ethmoid sinus, maxillary sinus, and sphenoid sinus) were summed to derive a GOSS scale (range: 0–50 points) (Figure 1).

Statistical Analysis

Statistical analysis was performed using IBM SPSS statistical software version 26.0. Continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as the number (percentage) of the total population. The independent samples *t*-test was used for continuous variables that conformed to normal distribution between the osteitis and non-osteitis groups, and the $\chi 2$ test was used for categorical variables. Correlation analysis was performed using Spearman's analysis to show the correlation between the data. Binary logistic regression analysis was used for multivariate analysis of predictors and calculation of ratio ratios in the osteitis group, and subject operating characteristic curves were used to analyze the predictive ability of clinical parameters. $p < 0.05$ was considered statistically significant.

Result

Demographic Data

A total of 125 patients with CRSwNP who met the inclusion criteria were enrolled in this study and were divided into the osteitis group (n=69) and the non-osteitis group (n=56) according to the presence or absence of osteitis. The general clinical data characteristics are shown in Table 1, which shows that the prevalence of concomitant asthma in the patients

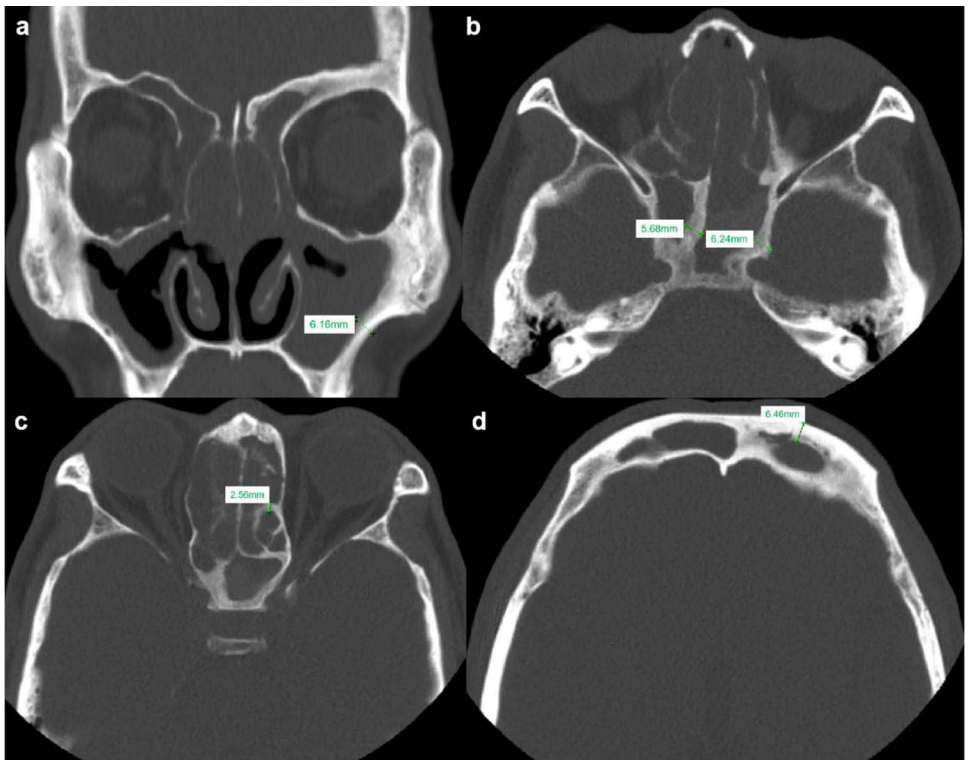

Figure 1 Radiological measurement using Global Osteitis score scale system for computed tomography of the paranasal sinuses. Measurement was made for hyperostosis area with maximal thickness of the osteitic focus in all the sinuses, for example (**a**) maxillary sinus (**b**) sphenoid sinus (**c**) ethmoidal sinus and (**d**) frontal sinus.

Table 1 Demographic Data of 125 Patients with CRSwNP

	Osteitis Group (n=69)	Non-Osteitis Group (n=56)	P
Men, n (%)	50.00(72.46%)	39.00(69.64%)	0.729
Age, years	43.48±12.63	43.80±14.33	0.894
Duration, years	6.78±8.70	6.54±7.15	0.866
Smoker, n (%)	14(22.29%)	13(23.21%)	0.693
Asthma, n (%)	19(27.54%)	5(8.93%)	0.009
Aspirin intolerance triad, n (%)	3(4.35%)	0.00	0.114
Allergic rhinitis, n (%)	41(59.42%)	30(53.57%)	0.512
Prior sinus surgery history, n (%)	16(23.19%)	10(17.86%)	0.465

in the osteitis group (27.54%) was significantly higher than that in the non-osteitis group (8.93%), and the difference was statistically significant (P=0.009). In contrast, there was no statistically significant difference in the comparison of gender, age, disease duration, smoking history, history of previous nasal surgery, allergic rhinitis, and aspirin intolerance triad between the osteitis and non-osteitis groups. SNOT-22 scores, LUND-MAKAY scores, and LUND-KEDENY scores were significantly higher in the osteitis group than in the non-osteitis group, and the difference was statistically significant ($P < 0.001$) (Figure 2).

Eosinophils and Type 2 Inflammatory Mediators in Osteitis and Non-Osteitis Groups

In terms of eosinophils, the absolute value of tissue eosinophils in the osteitis group (32.06±37.13/HPF) was significantly higher than that in the non-osteitis group (19.39±28.03/HPF), and the difference was statistically significant (P<0.05). There was no significant difference between the two groups in terms of the absolute value of blood eosinophils (P=0.35). In terms of type 2 inflammatory mediators, IL-13 and periosteal proteins were significantly higher in the osteitis group compared with the non-osteitis group, and the difference was statistically significant (P<0.001). Comparison of IL-4 and IL-5 between the two groups showed no statistically significant difference (Figure 2).

Correlation Between Severity of Osteitis and Clinical Indicators

Correlation analysis of various clinical indicators with the GOSS score revealed that the LUND-MAKAY score and LUND-KEDENY score were positively correlated with the GOSS score (r=−0.477 and 0.515, P<0.001). In terms of type 2 inflammatory mediators, only periosteal proteins were found to be positively correlated with the GOSS score (r=0.334, P=0.005). The tissue eosinophil count was positively correlated with the GOSS score (r=0.246, P=0.042), see Figure 3.

Logistic Regression Analysis

Variables with significant differences between osteitis and non-osteitis groups, including asthma, SNOT-22 score, LUND-MAKAY score and LUND-KEDENY score, nasal secretion IL-13, nasal secretion periosteal protein, and absolute value of tissue eosinophils were included in logistic regression analysis, which showed that IL-13 and periosteal protein were CRSwNP osteitis independent risk factors ($P < 0.001$) (Table 2).

ROC Curves and Sensitivity and Specificity of Each Predictor

Figure 4 shows the receiver operating characteristic curve (ROC) of subjects for asthma, SNOT-22 score, LUND-MAKAY score LUND-KEDENY score, IL-13, osteoprotegerin, and absolute tissue eosinophil values. The area under the curve (AUC) values for each clinical parameter are shown in Table 3, except for asthma, all the other six had clinical predictive value, and their optimal cut-off values, sensitivity, and specificity were calculated (Table 4), of which nasal

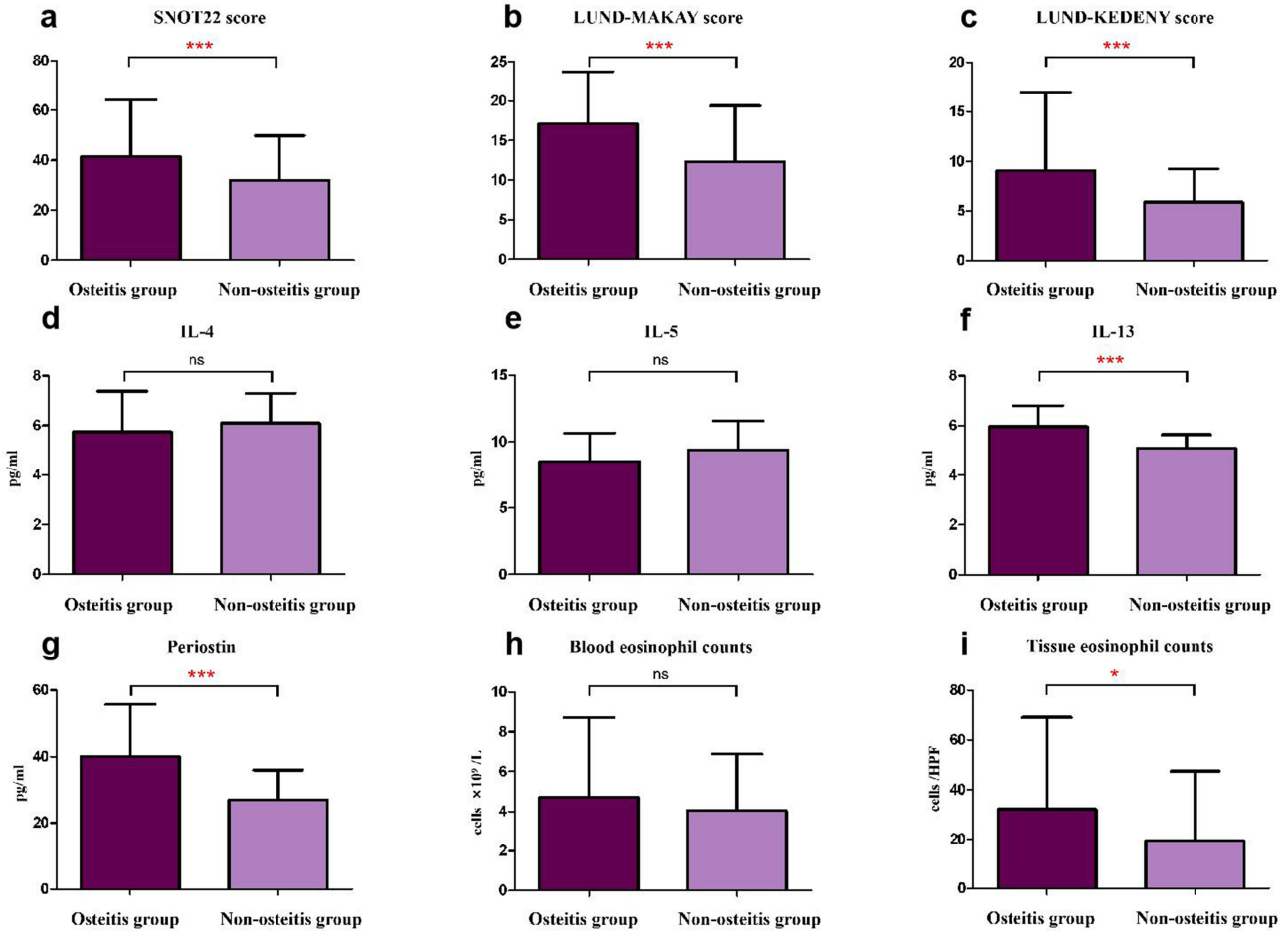

Figure 2 (**a-i**) indicate that SNOT22 score, LUND-MAKAY score, LUND-KEDENY score, IL-4, IL-5, IL-13, periostin, blood eosinophil counts, tissue eosinophil counts in osteitis and non-osteitis groups. ns=no significance*P < 0.05. ***P < 0.001.

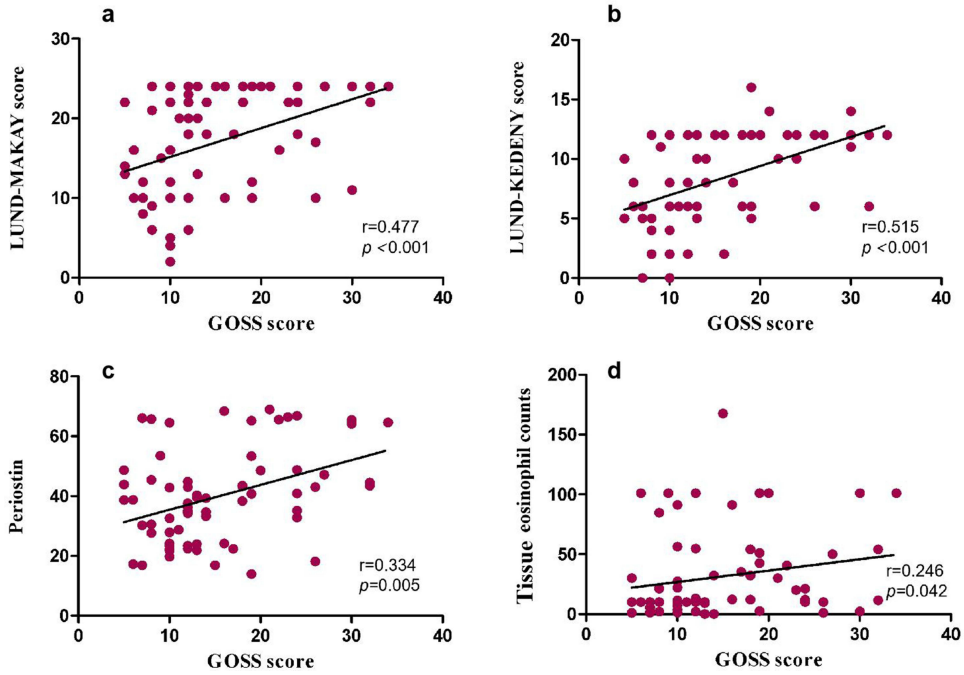

Figure 3 (**a-d**) indicate that osteitis GOSS correlates with LUND-MAKAY score, LUND-KEDENY score, periostin and tissue eosinophils, respectively.

Table 2 Multivariate Logistic Regression Analysis of the Predictive Factors for Osteitis Group

	OR	95% CI	P
Asthma	1.007	0.16–6.33	0.994
IL-13	27.924	7.583–102.828	<0.001
Periostin	1.201	1.105–1.306	<0.001
SNOT-22 score	1.035	0.996–1.075	0.079
LUND-MAKAY score	1.07	0.955–1.199	0.242
LUND-KEDENY score	1.245	0.992–1.561	0.059
Tissue eosinophil counts	0.997	0.976–1.019	0.785

Abbreviations: OR, odd ratio; CI, confidence interval.

secretion IL-13 had the highest predictive value (AUC=0.786), with a cut-off value of 5.8059pg/mL, sensitivity of 58.0% and specificity of 89.3%.

Discussion

Osteitis is a disease of inflammation and bone remodeling characterized primarily by the formation of new bone formation, which is also accompanied by mucosal thickening. However, controversy exists regarding the exact mechanism of action of osteitis in CRS, and many studies have shown a correlation between CRS disease severity and osteitis. In terms of quality of life, although the use of the nasal component of the Rhinosinusitis Outcome Measure (RSOM-31) score did not find evidence of a positive correlation between osteitis and disease severity in a previous study,[12] our study found that patients with CRSwNP with concomitant osteitis tended to have more severe subjective symptoms and poorer quality of life outcomes.

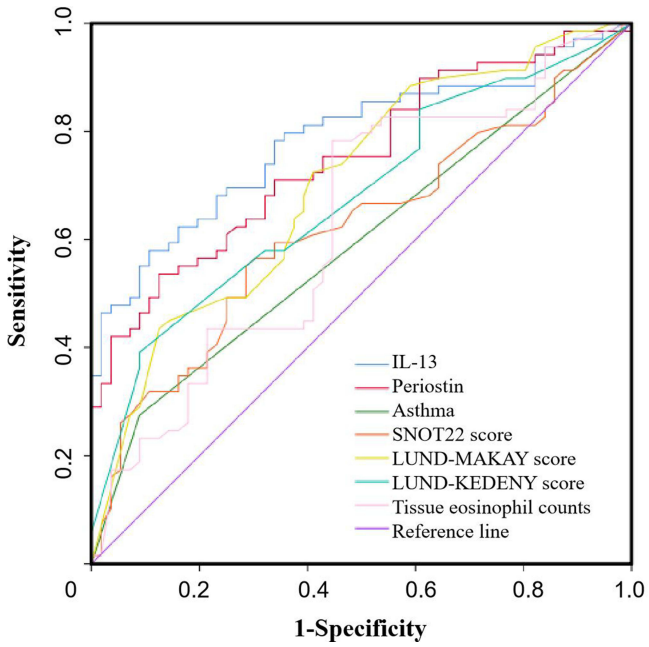

Figure 4 The receiver operating characteristic curve (ROC) of subjects for asthma, SNOT-22 score, LUND-MAKAY score and LUND-KEDENY score, IL-13, periostin, and tissue eosinophil counts.

Table 3 ROC Analysis of Results for Patients with Osteitis

	AUC	95% CI	P
Asthma	0.593	0.494–0.692	0.074
IL-13	0.786	0.707–0.866	<0.001
Periostin	0.751	0.667–0.835	<0.001
SNOT-22 score	0.62	0.522–0.718	0.021
LUND-MAKAY score	0.703	0.612–0.794	<0.001
LUND-KEDENY score	0.678	0.585–0.771	0.001
Tissue eosinophil counts	0.63	0.53–0.729	0.013

Abbreviations: AUC, area under curve; CI, confidence interval.

Table 4 Sensitivity and Specificity of IL-13 and Periostin for Osteitis

	Cut-Off Point	Sensitivity (%)	Specificity (%)
IL-13	5.8059	0.58	0.893
Periostin	38.2651	0.536	0.875
SNOT-22 score	36.5	0.551	0.449
LUND-MAKAY score	11.5	0.725	0.589
LUND-KEDENY score	9	0.478	0.522
Tissue eosinophil counts	9.9	0.783	0.217

Patients with sinusitis combined with osteitis are often accompanied by allergic or atopic diseases, and asthma has been found to be an important factor in the high prevalence of osteitis in patients with CRS. Patients with osteitis in our study had an increased prevalence of concomitant asthma. Asthma is an allergic disease that may not contribute directly to the pathogenesis of osteitis, but it may play a modifying role in which osteitis occurs, as they are associated with more severe mucosal and bone inflammation.[13] In clinical presentation, patients with CRSwNP with osteitis had more severe inflammatory manifestations on endoscopy, such as swelling and thickening of the mucosa, and in radiology, the degree of osteitis correlated with the Lund-Mackay score, which is consistent with previous studies.[14–16] Many studies have found a higher probability of osteitis in patients with previous revision surgery for sinusitis, which may be related to the fact that stripping the mucosa or periosteum during multiple surgeries can also lead to underlying bone changes,[17] and the patients with osteitis in our study also had a higher history of revision surgery. Therefore, osteitis may be an important factor leading to the deterioration of CRS disease and then progressing to refractory CRS disease, and it is particularly important to further search for mechanisms and biomarkers of inflammation involving the mucosa and underlying bone.

Mucosal inflammation around sinus bone and the inflammatory microenvironment of nasal mucus plays a crucial role in osteitis formation, but the underlying immunologic and molecular mechanisms remain to be elucidated. Bacterial infection is considered to be an important factor in bone proliferation following infection, and in recent years, immune cells and the inflammatory mediators they secrete have come into focus in the formation of osteitis in CRS.The inflammatory endotypes of CRS are categorized as either type 2 or non-type 2 according to the underlying immune molecular mechanisms, and many studies have shown that the pathogenesis of CRSwNP is related to type 2 inflammation-mediated immune responses.[2] Eosinophils are important cells in the type 2 inflammatory response. Many studies have found that eosinophils have an important role in osteitis and it was found that blood and sputum levels of

eosinophils in asthmatic patients were directly associated with the thickening of sinus mucosa and osteitis.[18] Snidvongs et al[6] suggested that osteitis was associated with increased tissue and serum eosinophils in patients with eosinophilic rhinosinusitis and our study also proved that tissue eosinophils were significantly increased in patients with CRSwNP with osteitis. The severity of osteitis showed a positive trend of correlation with tissue eosinophils. Wang et al evaluated sieve bone samples from 39 patients with CRS and found that eosinophils infiltrated the periosteum and induced TGF-β1 expression, periosteal thickening, increased osteoclast activity, and de novo bone production.[19] Studies have shown that sinus mucosal eosinophils activation releases Th2-type inflammatory cytokines into the circulation, inducing eosinophils to be systemically recruited to the mucosa and even bone in the sinuses, exacerbating inflammation of the sinus mucosa and the formation of osteitis[20,21].

The interaction of various inflammatory cytokines in the inflammatory environment of the nasal cavity and sinuses affects bone remodeling. Bone remodeling is a physiological process in which there is a continuous balance between osteoclast and osteoblast activity, and in the presence of severe persistent mucosal inflammation, the balance between osteoclast bone formation and osteoclast resorption may be disrupted, resulting in the generation of new bone.[22] Our study found that IL-13, an inflammatory mediator in the nasal mucus microenvironment, was highly expressed in patients with osteitis and had a predictive value for the development of osteitis in patients with CRSwNP. IL-13 are both representative type 2 inflammatory cytokines, which can disrupt homeostasis by inhibiting bone resorption through inhibition of COX-2-dependent prostaglandin synthesis in osteoblasts. Neogenesis in CRS seems to have a potential pathophysiologic link with IL-13[23]. Khalmuratova et al[24] found that IL-13 expression was up-regulated in CRS patients with sinus neogenesis and that IL-13-induced RUNX2 promoted new bone formation in CRS patients through its effect on osteoblast activity. These studies suggest that IL-13 in either mucosa or mucus is an important biomarker of de novo bone formation in CRS.

In recent years, the association of osteoblasts with type 2 inflammatory diseases such as asthma and sinusitis has gained increasing attention.[25] Osteoprotegerin, initially known as osteoblast-specific factor 2 osteoblast-specific factor 2, has been shown in vitro to act on bone formation by increasing osteoblast proliferation, differentiation, adhesion, and survival.[26] Studies have shown that osteopontin plays an important role in type 2 CRS,[27] and more upregulation of osteopontin was observed in nasal polyp tissues of CRSwNP patients.[28] Periosteal proteins are induced by IL-4 and IL-13 secreted by epithelial cells and mediate eosinophilic infiltration and tissue fibrosis,[29] which may be related to our previous elaboration that tissue eosinophilia leads to altered bone remodeling. In our study, osteoprotegerin levels in nasal mucus were found to be highly expressed in patients with osteitis, and osteoprotegerin and GOSS scores were positively correlated. However, osteoprotegerin (AUC value of 0.751) had a lower predictive ability for osteitis formation in sinusitis compared to IL-13 (AUC value of 0.786). The present study is leading in demonstrating that high expression of periosteal proteins has an important role in osteitis, and further studies on the underlying pathophysiologic mechanisms are still needed.

This is a cross-sectional observational study that only reviewed CRSwNP patients from a single center in our hospital, and future studies are needed in more centers and different ethnic populations. Only type 2 inflammatory cells and mediators were collected and analyzed in this study, and whether other non-type 2 inflammation is involved in osteitis formation still deserves further study.

Conclusion

Osteitis is associated with severe symptoms and endoscopic manifestations of CRSwNP. Elevated nasal secretion IL-13, periosteal proteins, and tissue eosinophils contribute to osteitis formation.

Ethics Approval and Informed Consent

All procedures performed and data collected in this study adhered to the guidelines of the Declaration of Helsinki committees. The study was approved by the Ethics Committee of the Peking University Third Hospital (Ethics Committee Approval No. 005-01). Written consent was obtained from each patient.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Shi JB, Fu QL, Zhang H, et al. Epidemiology of chronic rhinosinusitis: results from a cross-sectional survey in seven Chinese cities. *Allergy*. 2015;70(5):533–539.
2. Fokkens WJ. EPOS2020: a major step forward. *Rhinology*. 2020;58(1):1.
3. Bhattacharyya N. Surgical treatment of chronic recurrent rhinosinusitis: a preliminary report. *Laryngoscope*. 2006;116(10):1805–1808.
4. Soler ZM, Hwang PH, Mace J, Smith TL. Outcomes after middle turbinate resection: revisiting a controversial topic. *Laryngoscope*. 2010;120(4):832–837.
5. Sacks PL, Snidvongs K, Rom D, Earls P, Sacks R, Harvey RJ. The impact of neo-osteogenesis on disease control in chronic rhinosinusitis after primary surgery. *Int Forum Allergy Rhinol*. 2013;3(10):823–827.
6. Snidvongs K, McLachlan R, Chin D, et al. Osteitic bone: a surrogate marker of eosinophilia in chronic rhinosinusitis. *Rhinology*. 2012;50(3):299–305.
7. Fokkens WJ, Lund VJ, Mullol J, et al. EPOS 2012: European position paper on rhinosinusitis and nasal polyps. A summary for otorhinolaryngologists. *Rhinology*. 2012;50(1):1–12.
8. Zhang Z, Liu J, Xie L, Cao W, Ma F, Zhang Y. Tissue eosinophils and mucous inflammatory cytokines for the evaluation of olfactory recovery after endoscopic sinus surgery in patients with nasal polyposis. *Am J Otolaryngol*. 2022;43(5):103561.
9. Hopkins C, Gillett S, Slack R, Lund VJ, Browne JP. Psychometric validity of the 22-item Sinonasal Outcome Test. *Clin Otolaryngol*. 2009;34(5):447–454.
10. Hudon MA, Wright ED, Fortin-Pellerin E, Bussieres M. Resection versus preservation of the middle turbinate in surgery for chronic rhinosinusitis with nasal polyposis: a randomized controlled trial. *J Otolaryngol Head Neck Surg*. 2018;47(1):67.
11. Lund VJ, Kennedy DW. Staging for rhinosinusitis. *Otolaryngol Head Neck Surg*. 1997;117(3 Pt 2):S35–40.
12. Georgalas C, Videler W, Freling N, Fokkens W. Global Osteitis Scoring Scale and chronic rhinosinusitis: a marker of revision surgery. *Clin Otolaryngol*. 2010;35(6):455–461.
13. Mohamad NS, Mohamad S, Aziz ME, Abdullah B. The Effect of Atopy on the Incidence of Osteitis in Patients with Chronic Rhinosinusitis. *J Inflamm Res*. 2022;15:1017–1026.
14. Lee JT, Kennedy DW, Palmer JN, Feldman M, Chiu AG. The incidence of concurrent osteitis in patients with chronic rhinosinusitis: a clinicopathological study. *Am J Rhinol*. 2006;20(3):278–282.
15. Bhandarkar ND, Mace JC, Smith TL. The impact of osteitis on disease severity measures and quality of life outcomes in chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2011;1(5):372–378.
16. Huang Z, Hajjij A, Li G, Nayak JV, Zhou B, Hwang PH. Clinical predictors of neo-osteogenesis in patients with chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2015;5(4):303–309.
17. Bhandarkar ND, Sautter NB, Kennedy DW, Smith TL. Osteitis in chronic rhinosinusitis: a review of the literature. *Int Forum Allergy Rhinol*. 2013;3(5):355–363.
18. Mehta V, Campeau NG, Kita H, Hagan JB. Blood and sputum eosinophil levels in asthma and their relationship to sinus computed tomographic findings. *Mayo Clin Proc*. 2008;83(6):671–678.
19. Wang M, Ye T, Liang N, et al. Differing roles for TGF-β/Smad signaling in osteitis in chronic rhinosinusitis with and without nasal polyps. *Am J Rhinol Allergy*. 2015;29(5):e152–9.
20. Bousquet J, Van Cauwenberge P, Khaltaev N. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol*. 2001;108(5 Suppl):S147–334.
21. Togias A. Systemic effects of local allergic disease. *J Allergy Clin Immunol*. 2004;113(1 Suppl):S8–14.
22. Perloff JR, Gannon FH, Bolger WE, Montone KT, Orlandi R, Kennedy DW. Bone involvement in sinusitis: an apparent pathway for the spread of disease. *Laryngoscope*. 2000;110(12):2095–2099.
23. Oue S, Ramezanpour M, Paramasivan S, et al. Increased IL-13 expression is independently associated with neo-osteogenesis in patients with chronic rhinosinusitis. *J Allergy Clin Immunol*. 2017;140(5):1444–1448.e11.
24. Khalmuratova R, Shin HW, Kim DW, Park JW. Interleukin (IL)-13 and IL-17A contribute to neo-osteogenesis in chronic rhinosinusitis by inducing RUNX2. *EBioMedicine*. 2019;46:330–341.
25. Ohta N, Ishida A, Kurakami K, et al. Expressions and roles of periostin in otolaryngological diseases. *Allergol Int*. 2014;63(2):171–180.
26. Zhu S, Barbe MF, Liu C, et al. Periostin-like-factor in osteogenesis. *J Cell Physiol*. 2009;218(3):584–592.
27. Izuhara K, Fujieda S, Ohta N. The functional role and the clinical application of periostin in chronic rhinosinusitis. *Expert Rev Clin Immunol*. 2023;19(8):857–866.

28. Ishida A, Ohta N, Suzuki Y, et al. Expression of pendrin and periostin in allergic rhinitis and chronic rhinosinusitis. *Allergol Int*. 2012;61(4):589–595.
29. Takayama G, Arima K, Kanaji T, et al. Periostin: a novel component of subepithelial fibrosis of bronchial asthma downstream of IL-4 and IL-13 signals. *J Allergy Clin Immunol*. 2006;118(1):98–104.