BIOLOGY, MEDICINE, & NATURAL PRODUCT CHEMISTRY ISSN 2089-6514 (paper)
Volume 14, Number 1, April 2025 | Pages: 43-50 | DOI: 10.14421/biomedich.2025.141.43-50 ISSN 2540-9328 (online)

Correlation of BMP2 with Degree of Osteitisin Primary CRS with and without nasal Polyps

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Manuscript received: 07 November, 2024. Revision accepted: 17 February, 2025. Published: 28 February, 2025.

Abstract

Chronic rhinosinusitis (CRS) is an inflammation of the nasal mucosa and paranasal sinuses, persisting for over-12 weeks. CRS involves a remodeling process and opacification known as osteitis, resulting from type 2 and non-type two inflammation. Osteitis severity is assessed using CT scans and the Global Osteitis Scoring Scale (GOSS). Bone morphogenetic protein-2 (BMP-2) is crucial in osteogenesis and bone remodeling. However, no research has shown a relationship between BMP-2 concentration and osteitis degree, as measured by GOSS, in CRS patients with or without nasal polyps. The objective of this study is to analyze the relationship between BMP-2 concentration and osteitis degree measure with GOSS in primary CRS. A cross-sectional analytic observational study was conducted using primary RSK as the study population. BMP-2 concentration, a marker for bone remodeling, used ELISA. The osteitis of the paranasal sinus walls was assessed with a CT scan and quantified using the GOSS method. The study included 44 patients, with 8 of them serving as the control group. It was found that BMP-2 concentration (ng/mL) had a linear relationship with the GOSS degree in patients with CRS, showing a correlation of 0.583 (deviation >0.05). Further analysis revealed a significant correlation between BMP-2 concentration and GOSS, with a coefficient of 0.857 (considered very significant, in the range of 0.76-0.99). This strong correlation indicates that as BMP-2 concentration strongly correlates with the occurance of osteitis, which were measured by GOSS. BMP-2, as a marker for osteitis in CRS, shows a significant and linear correlation with the severity degree of osteitis measured by GOSS.

Keywords: BMP-2 Concentration; Chronic Rhinosinusitis; *Global Osteitis Scoring Scale*; Osteitis.

INTRODUCTION

The paranasal sinuses are air-filled cavities located within certain bones of the skull. Each side of the skull contains four paranasal sinuses: the frontal, maxillary, ethmoid, and sphenoid sinuses. Inflammation of the nasal mucosa and paranasal sinuses is known as rhinosinusitis. When symptoms persist for more than 12 weeks without complete resolution, the condition is classified as chronic rhinosinusitis (CRS) (Dhingra, 2021; Brandi, 2019).

Rhinosinusitis is a significant health issue worldwide. In the United States, CRS is one of the most common reasons patients seek medical attention. Around 0.5% of acute respiratory infections (ARIs) caused by viruses in the U.S. progress to rhinosinusitis. CRS impacts around 31 million individuals in the United States, constituting about 5% to 12% of the population, making it a significant global health issue (Amanda S. Battisti et al., 2020; Russell A. Faust. 2010. According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2012, the prevalence of CRS varies globally: 5.5% in Brazil, 8% in China, 11% in Europe and Korea, and 12% in the U.S (Fokkens et al., 2012). Data from the Indonesian Ministry of Health (DEPKES RI) in 2003 showed that nasal and sinus diseases ranked 25th among the top 50 diseases in Indonesia, with 102,817 outpatient cases. At Dr. Saiful Anwar Hospital, annual reports from the ENT clinic in 2021 indicated that CRS cases accounted for 29% of all rhinology patients. Some patients with CRS also exhibit inflammatory hyperplasia in the nasal cavity. Research in Korea found that the prevalence of CRS with nasal polyps is 2.7% among adults, with an incidence of 0.63%-0.83% in the general population (Soepardi & Iskandar, 2001).

EPOS 2020 categorizes CRS into primary and secondary types. Primary CRS is further divided based on location (unilateral or bilateral) and inflammation type (type 2 or non-type 2) (Fokkens et al., 2020). CRS involves remodeling and thickening of the paranasal sinus bones, a condition known as osteitis. This occurs due to type 2 and non-type 2 inflammatory reactions in the sinonasal mucosa. Osteitis features bone inflammation, neo-osteogenesis, and remodeling, involving osteoclasts in bone degradation and osteoblasts in bone replacement. Although the exact mechanism of

osteitis in CRS is not fully understood, persistent mucosal inflammation is believed to cause bone cell death, leading to neo-osteogenesis and bone thickening. Chronic inflammation, especially type 2, is also linked to nasal polyposis. Bone thickening in CRS with osteitis is associated with the runt-related transcription factor 2 (RUNX2), crucial for osteoblast induction, proliferation, and maturation (Khalmuratova et al., 2019). CRS patients with osteitis generally have a worse prognosis and a higher likelihood of postoperative recurrence compared to those without osteitis (Khalmuratova et al., 2019).

The degree of osteitis in CRS can be assessed through imaging and histopathology. Imaging is more commonly used in clinical settings due to its non-invasive nature. Computed tomography (CT) scans are frequently employed to evaluate osteitis in CRS (Khalmuratova et al., 2019). CT scan results are used to grade osteitis based on various scoring criteria, including the Kennedy Osteitis Score (KOS), Global Osteitis Scoring Scale (GOSS), and modified GOSS. GOSS is the most commonly used as it provides a detailed assessment of the involvement and thickness of the walls of 10 sinuses (Leung et al., 2016).

Bone morphogenetic protein 2 (BMP-2) is a multifunctional growth factor in the transforming growth factor-beta (TGF-β) superfamily. BMP-2 is vital for bone formation and remodeling through the regulation of osteoblasts and osteoclasts (Kim et al., 2021). It can also activate RUNX2 via the SMAD1 pathway. When BMP-2 docks with its receptor, it phosphorylates SMAD1, which then activates RUNX2, playing a crucial role in osteoblast induction, proliferation, and maturation (Cho & Kwun, 2018).

Currently, no studies have directly examined the relationship between BMP-2 levels and the degree of osteitis measured using GOSS in CRS patients with and without nasal polyps. Given the relationship between BMP-2 and RUNX2 and the role of RUNX2 in osteitis in CRS, this study aims to investigate the correlation between BMP-2 levels and the degree of osteitis measured using GOSS in CRS patients with and without nasal polyps. Understanding the relationship between BMP-2 levels and GOSS could lead to the development of targeted therapies for osteitis in chronic rhinosinusitis. This insight might also help prevent the recurrence of chronic rhinosinusitis after surgery.

PATIENTS AND METHODS

This cross-sectional study was carried out between May 1, 2022, and November 30, 2022, across various departments at Dr. Saiful Anwar General Hospital, including the local and central operating rooms of the Otorhinolaryngology Head and Neck Surgery Department, the Radiology Department, and the Biomedical Laboratory of the Faculty of Medicine at Universitas Brawijaya, Malang, Indonesia. The study received approval from the Medical Ethics Committee of Dr. Saiful Anwar General Hospital (No. 400/217/K.3/102.7/2022). The study population consisted of all patients from the Rhinology Division who were admitted to the medical ward of Dr. Saiful Anwar General Hospital during the study period.

The inclusion criteria for this study are adult CRS patients over 18 years old according to clinical criteria from the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020, CRS patients who have never undergone functional endoscopic sinus surgery (FESS) before, and who have not used corticosteroids or antibiotics within 4 weeks prior to specimen collection. Control patients over 18 years old diagnosed with a rhinology-related condition other than chronic rhinosinusitis, with or without polyps, who require surgical intervention. Exclusion criteria for this study are CRS patients involving only the posterior paranasal sinuses, patients who do not consent to participate in the study, and control patients under 18 years old, those with allergic rhinitis, or those who have used corticosteroids or antibiotics within 4 weeks before specimen collection.

Age, sex, main symptoms (nasal blockage/obstruction/congestion, nasal discharge, facial pain/pressure, reduction/loss of smell, patient complaints duration, biopsy of the uncinate process tissue were obtained. The uncinate process tissues were examined using enzyme-linked immunosorbent assay (ELISA) according to the GOSS method to determine the BMP-2 levels. The osteitis of the paranasal sinus walls was assessed with a CT scan and quantified using the GOSS method. CT scan of the paranasal sinuses was performed without contrast, using bone setting, with axial, coronal, and parasagittal slices, with a thickness of 1-3 mm per slice, each component and the total GOSS were calculated using the HOROS 3.3.6 software.

Data were analyzed using the Spearman correlation test with a 95% Confidence Interval (CI) and an alpha level (α) of 0.05. Results are considered significant if $p<0.05$. This analysis uses Statistical Package for the Social Sciences (SPSS) 25.0.0 for Windows software.

RESULTS AND DISCUSSION

Result

A total of 33 patients with primary CRS and eight subjects as control were included in this study, with the age ranging from 18 to 68 years old and a mean age of 38,36 ± 15,272 years. There were 12 males and 21 females. The main symptoms observed among the patients were nasal blockage, nasal discharge, headache, facial pain, periorbital edema, and anosmia at 54.5%, 24.2%, 12.1%, 6.1%, 3%, and 0%. The complaints ranged from 12 to 416 weeks, with a mean duration of

91.21 ± 109.99 weeks. Bilateral paranasal sinus involvement was observed in 22 samples (66.67%), while unilateral involvement was observed in 11 samples (33.33%). CRS without polyps was more prevalent, occurring in 17 samples (51.52%), compared to CRS with polyps.

The higher incidence of CRS in females can be attributed to anatomical and hormonal differences. Females typically have smaller sinus ostia than males, which may impair sinus drainage and contribute to CRS development. Smaller ostia increase the likelihood of obstruction and bacterial colonization in the paranasal sinuses. Additionally, females have significantly higher levels of estrogen compared to males, which may further influence the prevalence and pathophysiology of CRS.

CT scan of the paranasal sinuses was performed using a bone setting view, with axial, coronal, and parasagittal slices of 1-3 mm thickness, without contrast (**Figure 1**). Osteitis assessment was conducted on 10 sinuses: left and right maxillary, left and right anterior ethmoid, left and right posterior ethmoid, left and right sphenoid, and left and right frontal sinuses, using the Global Osteitis Scoring Scale (GOSS) on axial, coronal, and parasagittal slices. The lowest total GOSS score was 0, and the highest total score was 50. A higher GOSS score indicates more severe osteitis. GOSS scores were then categorized into four degrees: no osteitis (GOSS score <5), mild osteitis (GOSS score 5-20), moderate osteitis (GOSS score 20-35), and severe osteitis (GOSS score >35). Osteitis on CT scan was characterized by loss of bone definition, hyperostosis, new bone formation, or signs of heterogeneity in the walls of the paranasal sinuses.

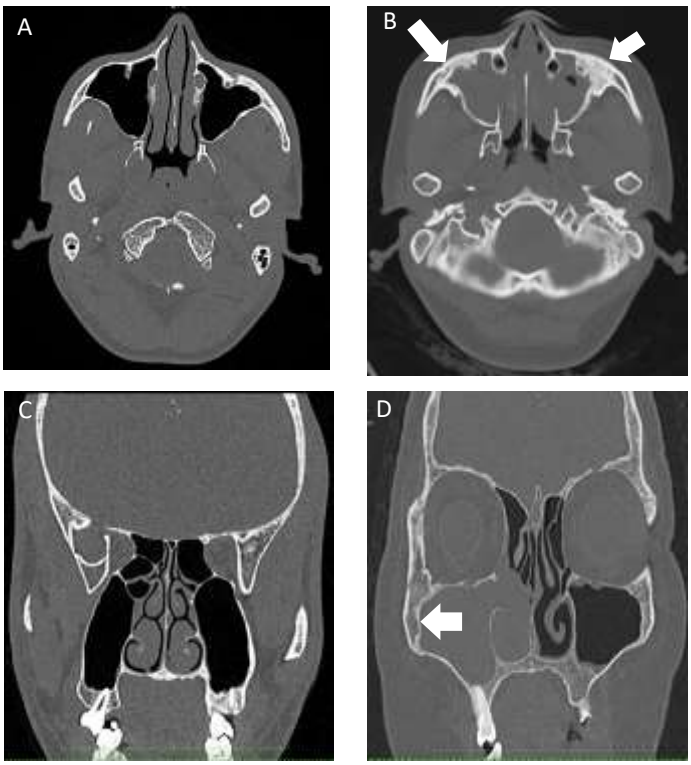

Figure 1. CT scan image of osteitis in various sections. The appearance of osteitis (loss of bone definition, hyperostosis, new bone formation, or signs of heterogeneity) on CT scan samples from CRS patients with osteitis is indicated by white arrows. **A-B** Axial sections of the maxillary sinus: **A** GOSS 0/0. **B** GOSS 5/5. C-D Coronal sections of the maxillary sinus.

In evaluating 330 paranasal sinuses, osteitis was detected in 168 cases (50.9%). The anterior ethmoid sinuses were the most frequently affected, accounting for 50 cases (29.8%), while the frontal sinuses exhibited the lowest incidence, with 17 cases (10.1%). The efficacy of osteitis detection was influenced by the type of CT scan slice. Axial slices proved to be the most effective, identifying osteitis in 80% of the cases involving the maxillary sinuses, corresponding to 36 pairs. Conversely, coronal slices demonstrated lower accuracy for osteitis detection in the paranasal sinuses, excep the sphenoid sinuses, where 18 cases (10.7%) were accurately detected using coronal slices (**Figure 2**).

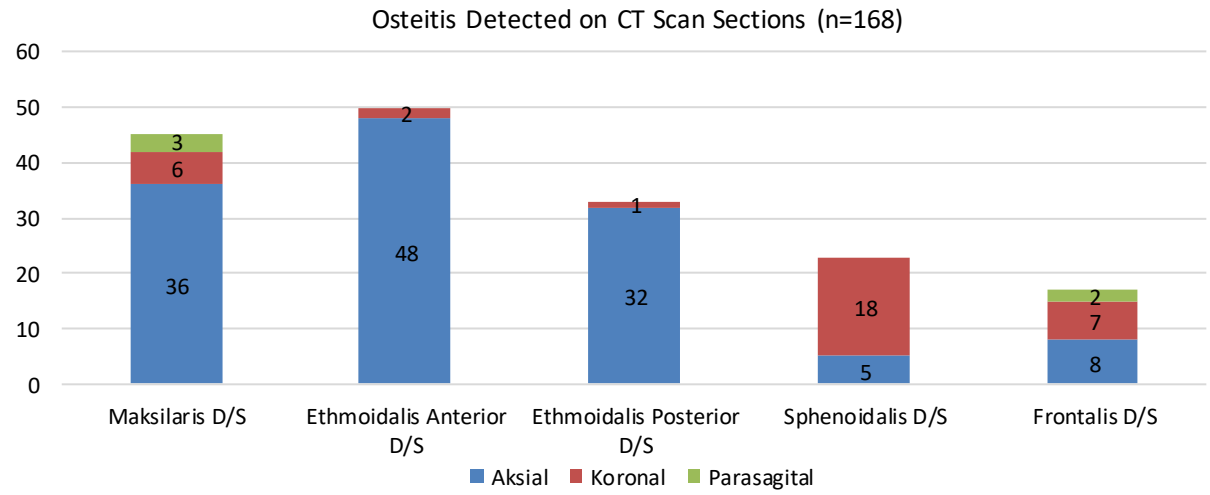

Figure 2. Distribution of Osteitis Detected in CT Scan Slices of CRS Patients. Blue bars denote the prevalence of osteitis in the paranasal sinuses detected on axial CT scan slices. Orange bars represent coronal slices, while gray bars correspond to parasagittal slices.

Figure 3 illustrates the distribution of osteitis severity within the RSK sample, indicating a predominance of mild osteitis cases (51.52%). Among these mild osteitis cases, seven patients had nasal polyps, while eight patients did not. For moderate osteitis (30.30%), nine patients were diagnosed with nasal polyps, and two patients were without nasal polyps. In cases of severe osteitis (3.03%), all patients had nasal polyps. Additionally, 15.15% of the RSK sample had no osteitis.

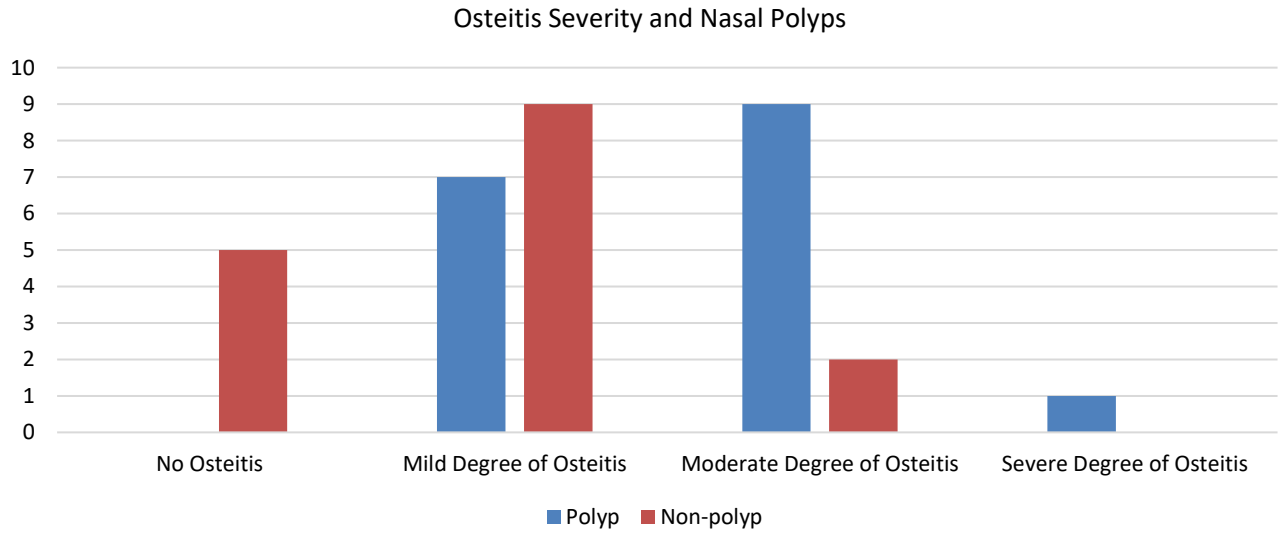

Figure 3. Distribution of Osteitis severity in CRS patients as measured with GOSS.

In this study, a total of 17 chronic rhinosinusitis samples with polyps and 16 samples without polyps were analyzed. The mean concentration of BMP2 in chronic rhinosinusitis samples with polyps was 3.78, with a standard deviation of 5.43. In contrast, the mean BMP2 concentration in samples without polyps was 1.30, with a standard deviation 5.43 (**Table 1**). This indicates that BMP2 levels are higher in chronic rhinosinusitis with polyps than those without.

Comparison analysis using the Mann-Whitney test, with significance set at $p<0.05$, yielded a p-value of 0.037 for BMP2 concentrations between chronic rhinosinusitis with and without polyps. This result indicates a significant difference, demonstrating an

association between elevated BMP2 levels and chronic rhinosinusitis, whether with or without polyps. However, the higher mean BMP2 concentration in samples with polyps suggests that this significant value reflects a more pronounced increase in BMP2 levels in chronic rhinosinusitis with polyps compared to those without.

Table 1. Comparative analysis of BMP2 levels in CRSwNP and CRSsNP.

BMP-2 Levels			
CRSwNP/CRSsNP	Mean	N	Std. Deviation
POLYP	3.78890152	17	5.439027531
NON POLYP	1.30166566	16	3.658008024
Total	2.58296898	33	4.759970211

Thirty-three samples meeting the inclusion criteria were assessed for osteitis severity using the Global Osteitis Scoring Scale (GOSS). The samples were divided into two groups based on the presence of nasal polyps: 17 samples with chronic rhinosinusitis with polyps and 16 samples with chronic rhinosinusitis without polyps. The mean GOSS score for chronic rhinosinusitis with polyps was 21.23, with a standard deviation 9.46. In contrast, the mean GOSS score for chronic rhinosinusitis without polyps was 10.56, with a standard deviation 7.75 (**Table 2**). Comparative analysis between chronic rhinosinusitis with and without polyps, based on GOSS scores, revealed a significant difference with a p-value of 0.002 ($p < 0.05$). This indicates that the presence of nasal polyps in chronic rhinosinusitis is associated with a higher GOSS score compared to cases without polyps.

Table 2. Comparison of GOSS scores in CRSwNP and CRSsNP.

GOSS			
CRSwNP/CRSsNP	Mean	N	Std. Deviation
POLYP	21.2353	17	9.46394
NON POLYP	10.5625	16	7.75430
Total	16.0606	33	10.11478

Disscussion

A total of 44 patients with Chronic Rhinosinusitis (CRS) who presented at the Otolaryngology Rhinology Clinic at RSSA were subjected to anamnesis and physical examination. Among these, 33 patients met the inclusion and exclusion criteria, and 8 patients were included as controls. Analysis of the sample's gender distribution revealed a predominance of females, with 21 (63.6%) female patients and 12 (36.4%) male patients. This finding aligns with prior research, which also identified a predominance of females among CRS patients, accounting for 63% of the 834 samples examined (De et al., 2019). This gender disparity is corroborated by data from the National Health Interview Survey (NHIS) in the United States, which reported that 63% of CRS patients were female. Similarly, a 2021 study conducted in Indonesia by Poluan and Marlina found that 73.2% of CRS patients were female, compared to 19% male patients. Epidemiological studies further indicate that CRS is nearly twice as prevalent in females as males.

The higher incidence of CRS in females can be attributed to anatomical and hormonal differences. Females typically have smaller sinus ostia as males, which may impair sinus drainage and contribute to CRS development. Smaller ostia increase the likelihood of obstruction and bacterial colonization in the paranasal sinuses. Additionally, females have significantly higher levels of estrogen compared to males, which may further influence the prevalence and pathophysiology of CRS (Hulse et al., 2014; Ference et al., 2015).

The sample population's age range varied from 18 to 68 years, with a mean age of 38.36 ± 15.27 years and a median age of 32 years. A prior study conducted in the United States demonstrated an increase in the prevalence of chronic rhinosinusitis (CRS) with advancing age, showing a 2.7% increase among individuals aged 20–29 years and a 6.6% increase among those aged 50–59 years. However, the prevalence decreased by 4.7% after the age of 60. Data from Dr. M. Djamil General Hospital in Padang, collected between January 1 and December 31, 2012, indicated that CRS was most prevalent among the young and adult age groups, accounting for 61.90% of cases. Similarly, research by the Rhinology Department of ENT-KL at FKUI RSCM reported the highest CRS prevalence in adults aged 18-75. The elevated incidence of CRS in adults is likely related to higher levels of social activity outside the home, which increases exposure to bacteria, viruses, and atmospheric

pollutants-environmental factors that play a significant role in the pathogenesis of CRS (Fokkens et al., 2012).

In this study, a correlation coefficient of 0.857 was observed, indicating a very strong positive association between BMP-2 concentration levels and GOSS. This positive coefficient suggests a direct relationship, where an increase in BMP-2 concentration is associated with a corresponding increase in GOSS levels. This finding aligns with earlier research by Kim *et al*., which showed a connection between BMP-2 levels and radiological findings. In their study, BMP-2 levels were measured using immunohistochemical staining, and the results demonstrated a significant correlation between BMP-2 and GOSS values ($p = 0.003$, $r = 0.332$). Because osteitis is frequently linked to the persistence of chronic rhinosinusitis (CRS), the study also explored this aspect and found that BMP-2 levels were associated with the refractoriness of the disease (Kim et al., 2021).

In this study, 33 samples that met the inclusion criteria were assessed for the degree of osteitis using GOSS. The samples were divided into two groups CRSwNP and CRSsNP. Of the total, 17 samples were classified as CRSwNP, and 16 were classified as CRSsNP. A comparative analysis was performed to evaluate the differences in GOSS scores between the two groups, revealing a statistically significant difference ($p = 0.002$). These findings support the hypothesis that the presence of nasal polyps in CRS cases is associated with an increased severity of osteitis. This may be attributed to the fact that both osteitis and CRSwNP share a similar inflammatory profile, specifically type 2 inflammation, characterized by a predominance of eosinophils in the chronic inflammatory process. This suggests that when managing patients with CRS, careful attention should be paid to the presence of nasal polyps, as this can significantly impact the severity of osteitis and provide insight into the underlying inflammatory burden. Recognizing the presence of nasal polyps in CRS patients is crucial in clinical practice. This awareness not only aids in accurately assessing the severity of osteitis using the GOSS score but also serves as an important indicator of the patient's overall inflammatory status. By considering these factors, clinicians can better tailor their therapeutic approaches to address the specific inflammatory mechanisms at play, potentially improving patient outcomes (Mehta et al., 2008).

The relationship between BMP-2 and osteitis begins with BMP-2 binding to its receptor, BMPR-2 monomer. This binding induces the dimerization of BMPR-2, which subsequently recruits BMPR-1 to transmit signals to molecules that regulate intracellular signaling. These molecules are SMAD 1/5/8. The BMP-2 complex with BMPR-2 and BMPR-1 phosphorylates SMAD 1/5/8. Phosphorylated SMAD 1/5/8 then binds to SMAD-4. This binding causes the phosphorylated SMAD 1/5/8 complex with SMAD-4 to enter the cell nucleus and activate RUNX2. The activation of RUNX2 induces osteocalcin (OCN), osteopontin (OPN), alkaline phosphatase (ALP), osteoprotegerin (OPG), matrix metallopeptidase 13 (MMP-13), and RANKL, which are involved in bone differentiation, formation, and turnover. RUNX2 is also known to induce the transcription factor Sp7, or Osterix (Sp7/Osx), which functions by activating OCN, OPN, bone sialoprotein, and type 1 collagen (Col1). These four proteins play a role in bone formation. Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are also induced by the phosphorylated SMAD 1/5/8 complex with SMAD-4. YAP/TAZ then enter the cell nucleus and bind to transcriptional enhancer activator domains (TEADs), which leads to the activation of Wnt family member 5a and 5b (Wnt5a/b), Dickkopf-related protein 1 (DKK-1), insulin-like growth factor binding protein-4 (IGFBP-4), and BMP-4. The activation of these proteins impacts the regulation between osteogenesis and osteoclastogenesis (Cho & Kwun, 2018; Paulini et al., 2021).

The relationship between BMP-2 and osteitis begins with BMP-2 binding to its receptor, the BMPR-2 monomer. This binding induces the dimerization of BMPR-2, which subsequently recruits BMPR-1, a receptor that transmits signals to intracellular signaling molecules. These molecules include SMAD 1/5/8. The BMP-2 complex with BMPR-2 and BMPR-1 phosphorylates SMAD 1/5/8. Phosphorylated SMAD 1/5/8 then binds to SMAD-4. This binding causes the phosphorylated SMAD 1/5/8 complex with SMAD-4 to enter the cell nucleus, activating RUNX2. The activation of RUNX2 induces the expression of osteocalcin (OCN), osteopontin (OPN), alkaline phosphatase (ALP), osteoprotegerin (OPG), matrix metallopeptidase 13 (MMP-13), and RANKL, which are involved in bone differentiation, formation, and turnover.

RUNX2 itself can also induce the transcription factor Sp7, also known as Osterix (Sp7/Osx), which functions by activating OCN, OPN, bone sialoprotein, and type I collagen (Col1). These four proteins play critical roles in bone formation. Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ) are also induced by the phosphorylated SMAD 1/5/8 complex with SMAD-4. YAP/TAZ then enter the cell nucleus and bind to transcriptional enhancer activator domains (TEADs), leading to the activation of Wnt family members 5a and 5b (Wnt5a/b), Dickkopf-related protein 1 (DKK-1), insulin-like growth factor-binding protein 4 (IGFBP-4), and BMP-4. The activation of these four proteins has implications for the regulation of osteogenesis and osteoclastogenesis (Cho & Kwun, 2018; Zhang et al., 2017).

In addition to the previously mentioned pathway, osteitis in CRS induced by BMP-2 can also be explained through the RUNX2 pathway. RUNX2 is a transcription factor that plays a crucial role in osteoblasts' induction, proliferation, and maturation. A study by Khalmuratova *et al*. demonstrated that the expression of RUNX2 is

elevated in osteoblasts of CRS patients with neo-osteogenesis. Moreover, RUNX2 can be induced by nasal tissue extracts from CRS patients exhibiting neo-osteogenesis. This increased expression of RUNX2 leads to the differentiation of osteoblasts, promoting neo-osteogenesis, a component of osteitis in CRS patients. The expression of RUNX2 is also correlated with higher Global Osteitis Scoring Scale (GOSS) scores, which are used to measure the extent of osteitis in CRS (Khalmuratova, 2019).

The RUNX2 pathway also promotes the expression of RANKL, a protein involved in bone formation, turnover, and differentiation. RANKL, a member of the tumor necrosis factor (TNF) family, plays a crucial role in the differentiation, survival, and activity of osteoclasts. RANKL binds to its specific receptor, RANK, on osteoclast progenitor cells, leading to the activation of osteoclasts and subsequent bone resorption. RANKL operates in opposition to osteoprotegerin (OPG), a soluble decoy receptor that binds to RANK. Both RANKL and OPG are induced by RUNX2, which is activated by BMP-2. Mature osteoblasts produce OPG, which competitively binds to RANK, thereby inhibiting bone resorption and allowing bone remodeling to occur.

RANKL expression is elevated in patients with CRS and is associated with osteitis and disease severity (Paulini, 2021). Immunohistochemical studies have shown a significantly higher distribution of RANKL-positive cells in the periosteum of CRS tissues compared to controls. Additionally, RANKL expression is higher in patients with recurrent CRS than in those with primary cases. Elevated RANKL levels contribute to the development of osteitis and may serve as a prognostic indicator in CRS. This suggests that the BMP-2 pathway may play a role in inducing osteitis in CRS patients. However, the relationship between OPG and osteitis in CRS has not yet been well-defined (Zhang et al., 2017; Cawley et al., 2020).

RANKL expression is elevated in patients with chronic rhinosinusitis (CRS) and is associated with osteitis and the severity of the disease. Previous immunohistochemical studies have shown a significantly higher distribution of RANKL-positive cells in the periosteum of CRS tissues compared to controls. Furthermore, RANKL expression is increased in patients with recurrent CRS compared to those with primary CRS. This elevation in RANKL contributes to the incidence of osteitis and could serve as a prognostic indicator in CRS. It is also suggested that RANKL may represent one of the pathways BMP-2 induces osteitis in CRS patients. However, there is currently no data on the relationship between osteoprotegerin (OPG) and osteitis in CRS (Kong, 2020).

BMP-2 is not typically produced under normal conditions; its production is primarily induced during inflammation in CRS. Factors influencing inflammation in CRS include genetic predisposition, microbial presence, and environmental conditions. Following sinonasal mucosal inflammation, thymic stromal lymphopoietin (TSLP) is induced, activating dendritic cells and subsequently T cells, leading to a T-helper 2 (TH2) immune response. TH2 cells produce interleukins such as IL-4, IL-13, and IL-5, resulting in the recruitment of eosinophils, neutrophils, and macrophages. BMP-2 production is influenced by inflammatory cytokines that regulate SMAD6 signaling, which in turn signals BMP-2, leading to bone remodeling and osteitis.Intrinsic mucosal inflammation causes mucociliary dysfunction due to direct damage and changes in mucus production. Mucosal ulceration leads to bacterial colonization and infection, which further enhances the inflammatory response and damages cilia function. Impaired mucociliary function fails to protect the mucosa from bacterial colonization, increasing exposure to eosinophilic mucus (Kim et al., 2021; Ahern & Cervin, 2019; Bachert & Tomassen, 2019).

CONCLUSSION

The degree of osteitis, as measured by the GOSS, is significantly higher in chronic rhinosinusitis with nasal polyps compared to those without nasal polyps. The significant increase in BMP-2 levels is strongly and positively correlated with the severity of osteitis, in patients with CRS.

Acknowledgements: The authors would like to express their sincere gratitude to all those who contributed to this research.

Authors' Contribution: Edi Handoko & David Santoso conducted the research and collected data. Iriana Maharani provided oversight of the study design and implementation. Yuyun Yueniwati P.W. offered additional guidance and support throughout the research process. Tanti Agustina assisted to drafting and revising the manuscript.

Competing Interests: The authors declare that there are no competing interests.

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