INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by polypoid mucosa, type 2 helper T-cell skewed immune profiles, and high recurrence. As a severe phenotype of chronic rhinosinusitis (CRS), CRSwNP greatly impairs quality of life with a prevalence of 1% to 4% in the US general population. Osteitis is a common feature of CRSwNP and refers to inflammation of the bone characterized by bone remodeling, neo-osteogenesis, and thickening of the adjacent mucosa. Recent studies have identified that osteitis is highly associated with disease severity and refractory CRS. Despite the evident associations between osteitis and CRS disease severity, basic research about the underlying molecular mechanisms of osteitis is lacking. A deeper understanding of the mechanisms governing the mucosal contribution to osteitis in CRSwNP is critical to improving therapeutic options and, ultimately, patient outcomes.

Previous studies have shown that osteitic bone in CRS is characterized by both osteoclastic bone resorption and osteoblastic bone formation. Bone morphogenetic proteins (BMPs) are known to regulate bone remodeling through the stimulation of osteoblasts and osteoclasts. Previous experimental studies have shown that altered levels of BMPs might contribute to bone and tissue remodeling in both allergic rhinitis and asthma. Furthermore, BMPs have previously been approved in patients with refractory chronic rhinosinusitis. The objective of this study was to explore the bone morphogenetic protein (BMP) pathway and to correlate the expression of key signaling molecules with the degree of osteitis in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).

Study Design: Prospective experimental analysis.

Methods: This was an institutional review board–approved study in which mucosal samples were obtained from sites of osteitis in CRSwNP and compared to nonosteitic healthy controls. Protein expression of key BMP pathway was quantified by aptamer–protein array and confirmed by a set of selected mRNA analyses. Degree of osteitis was assessed using both Kennedy Osteitis Score and Global Osteitis Score (GOS).

Results: Pro-osteoblastic expression of BMP7 (fold change [FC] = −1.18, P = .017) and BMP9 (FC = −1.32, P = .023), their receptors, BMP receptor type-1A (BMPR1A) (FC = −2.56, P = .005) and BMP receptor type-2 (FC = −1.28, P = .022), and two enhancers of BMP signaling pathway, the repulsive guidance molecule domain family member B (FC = −1.13, P = .008) and the chordin-like protein 1 (FC = −1.18, P = .027), were all significantly downregulated in CRSwNP. Conversely, the pro-osteoclastic factor, tetrathionate-resistant acid phosphatase type 5 (ACP5) (FC = 2.36, P = .001), was significantly increased in CRSwNP. GOS was inversely correlated with levels of BMP7 (r = −0.684, P = .005) and BMPR1A (r = −0.864, P = .005) and positively correlated with levels of ACP5 (r = 0.815, P = .004). The FCs among the proteins studied significantly and positively correlated with the FCs of their mRNA expression (r = 0.908, P = .002).

Conclusions: Downregulated pro-osteoblastic mucosal BMP signaling is strongly and significantly associated with increased osteitis in CRSwNP.

Key Words: Osteitis, chronic rhinosinusitis, nasal polyps, bone morphogenetic protein pathway.

Level of Evidence: NA
detected in nasal polyps suggesting the mucosa itself may be the critical driver of metaplastic bone formation.21

These previous findings led us to hypothesize that osteitis may result from an imbalance in bone production and resorption mediated through mucosal BMP signaling pathways. The aim of this study was to 1) to explore mucosal BMP signaling pathway protein expression in patients with CRSwNP validated by a set of selected mRNAs analyses and 2) identify potential associations of these signaling proteins with objective osteitis scores.

**MATERIALS AND METHODS**

This study was approved by the institutional review board at the Massachusetts Eye and Ear Infirmary. Tissue samples were obtained from patients undergoing endoscopic sinus surgery and had not been exposed to antibiotics or corticosteroids within the preceding 4 weeks. Inclusion criteria included patients diagnosed with CRSwNP according to the International Consensus Statement on Allergy and Rhinology22 and healthy patients (i.e., controls) undergoing surgery for noninflammatory disease (n = 10 per group). Patients with cystic fibrosis, ciliary dysfunction, autoimmune disease, or immunodeficiency were excluded. Additional exclusion criteria among controls included the presence of asthma or allergy. No current smokers were included in either the CRSwNP or control group. Atopy was diagnosed based on the positive skin tests. Demographic data were also collected. Radiographic severity and endoscopic severity were assessed according to the Lund-Mackay scoring scale23 and the Lund-Kennedy scale,24 respectively. Tissues were fixed and embedded in paraffin wax for routine hematoxylin and eosin staining to quantify tissue eosinophilia. The number of eosinophils per high-power field (HPF) was calculated according to Günel et al.25 Briefly, five fields were randomly selected per slide and scored by two independent observers.

**Total Protein Extraction and Quantitative Protein Analysis**

Mucosal samples from nasal polyps (among CRSwNP patients) or inferior turbinates (among control patients) were obtained during surgery. Samples for proteomic analysis were embedded in OCT compound (Thermo Fisher Scientific, Waltham, MA) and frozen at −80°C before analysis. The mucosal tissue was processed according to SomaLogic’s (Boulder, CO) guidelines. Briefly, embedded tissue was sectioned at 10 μm, and a total of 10 sections were collected in a frozen sterile Eppendorf tube. Halt Protease Inhibitor Cocktail (100 μl, Thermo Fisher Scientific) with T-PER (Tissue Protein Extraction Reagent; Thermo Fisher Scientific) was prepared according to the manufacturer’s instructions to extract the total protein from the tissue sections. The tissue sections were homogenized with a rotary pestle for 30 seconds and then centrifuged for 10 minutes at 14,000g, while at 4°C, to pellet cell debris. The supernatant was filtered through a 0.2-μm filter (Sartorius Minisart RC Syringe Filters, Thermo Fisher Scientific) before quantification of the total protein using the Micro BCA Protein Assay Kit (Thermo Fisher Scientific). Sample aliquots were stored at −80°C until the proteomic array was performed.

The SOMAscan proteomic array (SomaLogic) was performed at the Beth Israel Deaconess Medical Center Genomics, Proteomics, Bioinformatics, and Systems Biology Center; samples were quantified using the SOMAscan Assay Cells & Tissue Kit, 1.9k (SomaLogic) according to the recommended protocol. Three controls provided by the kit and one no-protein buffer control were run in parallel with the samples per plate. Median normalization and calibration of the SOMAscan data were performed according to the standard quality control protocols at SomaLogic as previously described.26 Hybridization control normalization, median signal normalization, and between-run calibration were employed to remove assay and sample bias, according to the SOMAscan standard operating procedures.

**Transcriptomic Analysis**

To obtain 150 ng of purified total RNA, RNA samples were prepared from matched tissue samples according to Illumina TruSeq Stranded mRNA sample preparation kit guidelines (Illumina, San Diego, CA). External RNA Controls Consortium RNA controls (Thermo Fisher Scientific) were added prior to Poly(A) selection providing additional control for variability. RNA quality score value was calculated by Caliper LabchipGXII (Perkin-Elmer, Waltham, MA) to assess RNA quality and insert size. Briefly, RNA quantity was determined by RiboGreen (Thermo Fisher Scientific), and samples were then sequenced using the Illumina HiSeq4000. Trimmed reads were aligned by HISAT27 (version 2.1.0), to the human reference genome (hg19). Binary alignment map files were converted from the output sequence alignment map (SAM) files and sorted using SAMtools. Relevant transcripts were derived from matched tissue samples to the proteomic dataset.

**Evaluation of the Osteitis**

Osteitis was scored radiologically using both the Global Osteitis Score (GOS)10 and Kennedy Osteitis Score (KOS) systems.2 The details of these two methods were described by Snidvongs et al.7 Sinus bone thickness > 3 mm at any location was defined as osteitis as shown in Figure 1. Briefly, all 10 sinuses (right and left frontal, anterior ethmoid, posterior ethmoid, maxillary, and sphenoid) were measured, and the slice having the maximum sinus wall thickness was defined. For the KOS system, each sinus was scored as 0 (<3 mm), 1 (3–5 mm), or 2 (>5 mm). Woven bone with thickened, irregular, and/or heterogeneous lining of the sinus walls were measured rather than the normal lamellar/cortical bony wall. The entire sinus was also weighted for GOS, and the scores ranged from 1 to 5 for each sinus as follows: grade 1: <50% of the sinus walls involved and osteitis <3 mm wide; grade 2: <50% of the sinus was involved and 3- to 5-mm width; grade 3: <50% of the sinus involved and wider than 5 mm, or >50% of the sinus wall involved and <3-mm-wide osteitic changes; grade 4: >50% of the sinus wall involved and 3 to 5 mm; and grade 5: >50% of the sinus wall and thicker than 5 mm.

**Statistical Analysis**

Protein expression profiling was conducted through SomaLogic’s SOMAscan platform27 for 1,319 proteins, which included 12 hybridization controls. According to the standard QC protocols at SomaLogic, all samples passed the established technical QC criteria. Differential protein expression was tested using a Student t test followed by the Benjamini-Hochberg procedure for multiple hypotheses testing correction. A false discovery rate (FDR) value of <0.05 was considered statistically significant. Spearman correlation analysis was performed using Morpheus software (https://software.broadinstitute.org/morpheus) after log2 transformation to create correlation matrices. Transcriptome assembly and gene expression quantification were performed using StringTie (version 1.3.3b; https://ccb.jhu.edu/software/stringtie/#install), and fragments per kilobase million were generated. Ballgown package in R version 2.0.0 statistical software was utilized to perform differential gene expression analysis between phenotypic groups.
For the patient demographic data, the two-sample t test was applied for continuous variables that followed a normal distribution. A nonparametric Mann-Whitney U test was applied for continuous variables that did not follow a normal distribution. The one-sample Kolmogorov-Smirnov test was used to test whether a continuous variable was normally distributed. Categorical variables were compared using the \( \chi^2 \) test. A \( P \) value of < .05 was considered statistically significant. Tests were performed using SPSS statistical software version 17.0 (IBM, Armonk, NY).

**Bioinformatic Analysis**

Interactive network, functional category, and canonical pathway analyses were performed using the Genemania (http://genemania.org) and Ingenuity Pathway Analysis (IPA) software tools (Qiagen, Hilden, Germany; http://www.ingenuity.com).

**RESULTS**

**Study Population and Demographics**

There were no significant differences between CRSwNP and control groups with respect to gender, atopy, race, aspirin-exacerbated respiratory disease, and prior sinus surgery (nasal endoscopic surgery for chronic rhinosinusitis). Compared with controls, age, comorbid asthma, Lund-Mackay scores, and Lund-Kennedy scores were significantly higher in the CRSwNP cohort (\( P = .029, < .001, < .001, \) and <.001, respectively). Tissue eosinophils per HPF, GOS, KOS, immunoglobulin E levels, and periostin (POSTN) were also significantly increased in patients with CRSwNP (all \( P < .001 \)) (Table I, Fig. 2).

### Bone Morphogenetic Protein Signaling Pathway Is Dysregulated in CRSwNP

The pro-osteoblastic BMP signaling pathway in tissue proteomic was found to be significantly altered in patients with CRSwNP relative to controls (\( P < .001 \)). Specifically, BMP7, BMP9 (also known as growth and differentiation factor 2 [GDF2]), BMP receptor type-1A (BMPR1A), and BMP receptor type-2 (BMPR2) were significantly decreased in patients with CRSwNP (\( P = .017, .023, .005, \) and .022, respectively).

### Table I. Patients Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CRSwNP, N = 10</th>
<th>Control, N = 10</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr, median (IQR)</td>
<td>45.00 (38.25–55.75)</td>
<td>35.00 (21.75–40.25)</td>
<td>.029</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (70.0)</td>
<td>5 (50.0)</td>
<td>.65</td>
</tr>
<tr>
<td>Atopy, n (%)</td>
<td>2 (20.0)</td>
<td>0 (0)</td>
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</tr>
<tr>
<td>Caucasian, n (%)</td>
<td>10 (100%)</td>
<td>10 (100%)</td>
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</tr>
<tr>
<td>AERD, n (%)</td>
<td>2 (20.0)</td>
<td>0 (0)</td>
<td>.47</td>
</tr>
<tr>
<td>Comorbid asthma, n (%)</td>
<td>8 (80.0)</td>
<td>0 (0)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Prior sinus surgery, n (%)( ^* )</td>
<td>3 (30.0)</td>
<td>0 (0)</td>
<td>.21</td>
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<tr>
<td>Lund-Mackay, median (IQR)</td>
<td>15.00 (11.75–18.00)</td>
<td>0</td>
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<tr>
<td>Lund-Kennedy, median (IQR)</td>
<td>6.00 (5.00–8.50)</td>
<td>0 (0–2.25)</td>
<td>&lt; .001</td>
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<tr>
<td>Tissue EOS/HPF, median (IQR)</td>
<td>31.00 (18.25–61.75)</td>
<td>0 (0–1.00)</td>
<td>&lt; .001</td>
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<tr>
<td>GOS, median (IQR)</td>
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<td>&lt; .001</td>
</tr>
<tr>
<td>KOS, median (IQR)</td>
<td>7.75 (6.13–10.25)</td>
<td>0</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*Comparisons between groups for categorical variables were made using the \( \chi^2 \) test. Comparisons of continuous variables between groups were carried out using the Mann-Whitney U test. A \( P \) value of < .05 was considered statistically significant.

\( ^* \) Prior sinus surgery included endoscopic sinus surgery for chronic rhinosinusitis.

AERD = aspirin-exacerbated respiratory disease; CRSwNP = chronic rhinosinusitis with nasal polyps; EOS/HPF = eosinophils/high power field; GOS = Global Osteitis Score; IQR = interquartile range; KOS = Kennedy Osteitis Score.

![Examples of osteitic bone in patients with CRSwNP, indicated by a white arrow in the coronal section of the computed tomography.](image-url)
the repulsive guidance molecule domain family member B (RGMB) and the chordin-like protein 1 (CHRDL1), two enhancers of the BMP signaling pathway,\textsuperscript{28,29} were both significantly decreased in patients with CRSwNP (\(P = .008\) and \(.027\), respectively). Conversely, we also found that the level of tartrate-resistant acid phosphatase type 5 (ACP5), a pro-osteoclastic factor, was significantly increased in CRSwNP (\(P = .001\)) (Fig. 2).

An independent Genemania analysis of the significantly downregulated proteins confirmed the predicted functional consequences of BMP signaling pathway (Fig. 3). The most significantly dysregulated functions were confirmed as BMP signaling pathway (FDR value = \(9.34 \times 10^{-32}\)) and ossification (FDR value = \(2.84 \times 10^{-18}\)).

**Validation of Proteomic Results**

To independently validate the quantitative protein data, we analyzed the pattern of the related mRNA expression from the matched tissue mRNA dataset.
(Table II), which was derived from the whole transcriptome data. We found that the reported proteomic fold changes (FC) among BMPR1A (FC = −2.56), BMP9 (also known as GDF2) (FC = −1.32), BMP7 (FC = −1.28), BMP7 (FC = −1.18), CHRDL1 (FC = −1.18), RGMB (FC = −1.13), ACP5 (FC = 2.36), and POSTN (FC = 3.95) strongly (Pearson, r = 0.908) and significantly (P < .002) correlated the selected tissue mRNA, thereby confirming the validity of the proteomic results (Fig. 4).

Osteitis Scores Correlate With BMP Signaling Among Patients With CRSwNP

Our correlation analysis showed that BMPR1A, BMP7, and CHRDL1 generally negatively correlated with ACP5, KOS, and GOS with the strongest correlation being BMPR1A and GOS (Spearman, r = −0.864, P = .001) (Fig. 5). There were significant and positive correlations among BMPR2, BMP9, and RGMB, with the highest correlation being BMPR2 and BMP9 (r = 0.961, P < .001). Similarly, there were significant and positive correlations among ACP5, KOS, GOS, ephrins per HPF, and IgE, with the highest correlated being BMPR2 and BMP9 (r = 0.929, P < .001).

DISCUSSION

Osteitis is a common feature in CRSwNP and is predictive of greater disease severity and a propensity for recurrence.30 Infected mucosa has been shown to be capable of inducing periosteal reaction and subsequent bone changes, suggesting that mucosal inflammation is a key driver of adjacent bone metaplasia.31–33 Although mediators released from diseased mucosa have been implicated in increased osteoblastic/osteoclastic activity,34,35 the underlying molecular mechanisms underpinning this bone remodeling are not clear.

This study utilized quantitative multiplexed protein arrays to study biologically relevant alternations in specific bone remodeling related proteins in tissue, which may contribute to the osteitis in CRSwNP. Our analyses confirmed that the BMP signaling pathway was significantly altered and highly associated with osteitis. BMPs are cytokines belonging to the transforming growth factor–β superfamily, which carry out multiple functions during development including the regulation of the bone homeostasis (Fig. 6).36 There are four different subfamilies of BMP ligands according to their sequence similarity and function,37 and almost exclusively display osteogenic properties.17,38,39 BMP7 and BMP9 belong to group II and III, respectively. BMPs bind to BMP receptor types I and II, and their signal is mediated by phosphorylation of receptor-regulated Smads.30

In the present study, we found that mucosal BMP7, BMP9, and their receptors (BMPR1A and BMPR2) were all significantly downregulated in tissue. These findings harmonize with previous experimental studies demonstrating a significant reduction of BMPs in a mouse...
model of allergic rhinitis. Similarly, expression levels of BMP7 and BMP receptors have been shown to be significantly reduced in asthmatic patients. Our findings are the first to show these effects within nasal polyp tissue, and suggest that BMP signaling may play a role in the unified airway hypothesis.

In addition to a downregulation of BMP7 and BMP9 and their associated receptors, we also found that two enhancers of BMP signaling pathway, namely RGMB and CHRDL1, were also significantly decreased in tissue. These findings point to a generalized reduction in pro-osteoblastic activity in CRSwNP. Furthermore, our results show that tartrate-resistant ACP5, a bone resorption marker, is significantly increased. ACP5 is a functional protein utilized by osteoclasts to remove bone, and high ACP5 expression has been previously associated with increased rates of bone turnover.

Having demonstrated a significant suppression of the BMP signaling pathway, we next explored whether expression levels could be correlated with objective measures of osteitis. The levels of BMRP1A, BMP-7, and CHRDL1 negatively correlated with GOS, with the greatest inverse correlation being between BMRP1A and GOS \((r = -0.864, P = .001)\). Similarly, KOS was inversely correlated with the levels of BMRP1A and CRDL1. As a negative regulator of bone formation and marker of bone resorption, the level of ACP5 significantly and positively correlated with osteitis scores. Taken together, these findings cast a new light on osteitis and neo-osteogenesis in CRSwNP, suggesting that the underlying mechanism is one of dysregulated bone turnover as opposed to enhanced bone production.

The present study had several limitations. The sample size was relatively small, which may have limited the number of significantly dysregulated proteins that reached statistical significance using the conservative Benjamini-Hochberg procedure. Additionally, due to technical considerations, we restricted our analysis to the diseased mucosal tissue as opposed to the bone itself. However, as previously noted, multiple previous studies have established that the mucosa is an important regulator of underlying bone

<table>
<thead>
<tr>
<th>Ensembl Gene ID</th>
<th>Gene Symbol</th>
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<td>ENSG00000174136</td>
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<td>ENSG00000133110</td>
<td>POSTN</td>
<td>Periostin</td>
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</table>

BMP = bone morphogenetic protein.
Fig. 5. Spearman correlation matrix between BMP signaling proteins and osteitis scores among patients with CRSwNP (numbers represent \( P \) values among the all correlations with \( P < .05 \)). Spearman correlation analyses were performed after log2 transformation to create correlation matrices. A \( P \) value of < .05 was considered statistically significant. BMP5 = bone morphogenetic protein 5; BMP7 = bone morphogenetic protein 7; BMP9 = bone morphogenetic protein 9; BMPR1A = BMP receptor type-1A; BMPR2 = BMP receptor type-2; CHRDL1 = chordin-like protein 1; CRSwNP = chronic rhinosinusitis with nasal polyps; RGMB = repulsive guidance molecule domain family member B.

<table>
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<tr>
<th></th>
<th>BMPR1A</th>
<th>BMP-7</th>
<th>BMPR2</th>
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<th>GDF2/BMP9</th>
<th>BMP5</th>
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<th>GOS</th>
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<th>IGHE</th>
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<td>POSTN</td>
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Fig. 6. Graphical representation of the BMP signaling pathway in patients with osteitis and CRSwNP. Downregulated BMP signaling proteins included BMP7, BMP9, their receptors (BMPR1A and BMPR2), and two enhancers (RGMB and CHRDL1) together with upregulated ACP5 (a bone resorption marker) lead to the imbalanced bone turnover contributing to osteitis. BMP5 = bone morphogenetic protein 5; BMP7 = bone morphogenetic protein 7; BMP9 = bone morphogenetic protein 9; BMPR1A = BMP receptor type-1A; BMPR2 = BMP receptor type-2; CHRDL1 = chordin-like protein 1; CRSwNP = chronic rhinosinusitis with nasal polyps; RGMB = repulsive guidance molecule domain family member B.
Furthermore, the results of the whole transcriptome were not reported in the present study, and so the whole profiles of other significantly altered transcripts in CRSwNP were not accounted for. Finally, the tissue biopsies for mRNA evaluation contained several different cell types, which might have up- and downregulated transcripts in opposite directions, which may have masked some additional significant findings. Based on these findings, future studies will be focused on the effector cells and potential therapeutic implications.

CONCLUSION

To our knowledge, this is the first study to dissect the BMP signaling pathway in CRSwNP and correlate it with osteitis. Our results point to a new understanding of osteitis as a consequence of mucosal signaling driving abnormal adjacent bone turnover as opposed to new bone formation. Furthermore, the BMP signaling pathway may represent a potential therapeutic target when treating osteitis in patients with CRSwNP.

BIBLIOGRAPHY

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