

A Comparison of Sphenoid Sinus Osteoneogenesis in Aspirin-Exacerbated Respiratory Disease

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


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Abstract

Background: Aspirin-exacerbated respiratory disease (AERD) is characterized by excessive leukotriene production, diffuse polyp burden and osteitic bone changes. These bony changes have not been previously characterized.

Objective: The aim of this radiographic study is to characterize the bony changes noted on computed tomography (CT) scans of the sphenoid sinus in patients with AERD compared to other diseased sinonasal inflammatory states and non-diseased controls.

Methods: A retrospective review of 43 patients with clinically confirmed AERD were included and compared to 22 non-diseased, 9 allergic fungal sinusitis, and 43 chronic rhinosinusitis controls (23 without polyps and 18 with polyps). Comparative measurements were performed using fine-cut CT scans. Sites of comparison were the intersinus septum, the left and right lateral sphenoid wall, the roof, and left and right floor of the sphenoid sinus. Standardized measurements were averaged by two separate rhinologists.

Results: Patients with AERD had an average statistically significant increase in bone thickness compared to healthy and diseased controls in nearly every site with the most pronounced changes in the intersinus septum ($p < 0.05$).

Conclusion: Patients with AERD have significantly increased thickness of the sphenoid bone compared to control groups with the most pronounced difference in the intersinus septum. These findings may help clinicians increase suspicion for a diagnosis of AERD who clinically have diffuse nasal polyposis.

Keywords

aspirin exacerbated respiratory disease, AERD, asthma, bone remodeling, sinusitis, skull base, CRS, AFS, osteogenesis, sphenoid sinus

Introduction

Aspirin-Exacerbated Respiratory Disease (AERD) is characterized by asthma, nasal polyposis, and non-IgE mediated hypersensitivity to Aspirin and cyclooxygenase-1 inhibitors.^{1–3} Aberrant arachidonic acid metabolism produces excess leukotrienes which are potent proinflammatory mediators. An uninhibited leukotriene surge following the use of COX-1 inhibitors results in the exacerbated respiratory symptoms of rhinitis and asthma.¹

Patients with AERD develop a form of chronic rhinosinusitis (CRS) that progresses to severe

inflammation, mucosal edema, and nasal polyposis.² Previous studies have correlated AERD sinusitis with more advanced computed tomography (CT) staging

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scores secondary to diffuse mucosal inflammation.⁴ However, osteoneogenesis of the paranasal sinuses at distinct locations has not been evaluated. Previous studies have been limited to mucosal thickening changes on CT scans.

Currently there is emerging evidence of tissue remodeling in AERD caused by an influx of eosinophils and mast cells releasing leukotrienes both locally and systemically.⁵ Complementary mechanisms lead to a proliferation of collagen, recurrent local inflammatory responses, and fibrosis that affects the paranasal sinuses and lungs. Previous non-AERD sinusitis bone remodeling studies have found that recurrent infections and inflammatory episodes disseminate throughout the osteon and adjacent bony structures in the haversian bone system.³ There is subsequent widening of the haversian canal, remodeling, and increased vascularization all of which contribute to the thickening of the bone.³ Specific to AERD however, there have been no reports of bone remodeling despite the concurrent sinus inflammation as part of the triad.

We hypothesized that there would be evidence of bony changes within the sphenoid sinus through computed tomography (CT) scans in patients with AERD compared to non-diseased and diseased controls.

Materials and Methods

Study Group

Institutional review board approval was obtained from the University of North Carolina for this retrospective case-control study. The patients selected for review were evaluated via computed tomography (CT) imaging and treated for their disease status between January 2016 and September 2019. All study participants were between the ages of 17 and 85. Patients were selected during routine evaluation in the rhinology practice of a single tertiary care center. Diseased control populations consisted of patients demonstrating allergic fungal sinusitis (AFS), and Chronic Rhinosinusitis (CRS) with and without polyps.

AFS patients were included in the study following demonstration of the Bent-Kuhn criteria consisting of evidence of type I hypersensitivity, nasal polyposis, increased bone opacity on CT, eosinophilic mucus without fungal invasion of the sinonasal tissue, and positive fungal stain of sinus contents.⁶ CRS patients were included in the study if they demonstrated a diagnosis of CRS by symptomatology based on the American Academy of Otolaryngology – Head & Neck Surgery (AAO-HNS) CRS criteria and had supporting endoscopic or CT findings. Patients were then stratified to include only those with AERD. AERD was screened by the presence of asthma, CRS/nasal polyposis, and a

patient-reported sensitivity to aspirin. Patients with AERD gave an unambiguous history of asthma, respiratory symptoms that occurred within 2- 3 hours of ingestion of NSAIDs/Aspirin, and had endoscopic evidence of polyposis.

All patients diagnosed with AERD within the study time period were included for review. There was heterogeneity in the number of previous operations and medication regimens that limited further stratification.

The healthy control population consisted of patients who underwent CT scans for non-sinogenic indications including headache or skull base tumors not involving the sphenoid sinus. All scans were free of paranasal sinus mucosal thickening.

Computed Tomography Scans

A retrospective review of 43 patients with clinically confirmed AERD were compared to 22 non-diseased controls, 9 AFS, 18 CRS with polyps and 23 CRS without polyps using fine-cut coronal CT imaging. Images were obtained with 0.75 mm cut slices. Measurements of the intersinus septum, the left and right lateral sphenoid wall, the planum, and left and right floor of the sphenoid sinus were obtained at the same location of the sphenoid with a view of the Vidian canal and foramen rotundum (Figure 1). All measurements were performed independently by two rhinologists. The results were averaged for comparison. Measurements were made using computer-based imaging software.

Statistical Analysis

Summary statistics were calculated to describe the radiographic differences. A one-way ANOVA was used to compare measurements at the varying sites between AERD patients and controls. A p-value of less than 0.05 was considered statistically significant. All data analyses were performed in GraphPad Prism (San Diego, CA).

Results

The results of the CT imaging of the sphenoid sinus are presented in Table 1, which represents the average thickness measurements and confidence intervals across six different locations for given disease states. In the AERD group, the mean thickness of bones at the following site are as follows: intersinus septum 2.287 mm, left lateral sphenoid wall 1.992 mm, right lateral sphenoid wall 2.124 mm, left sphenoid floor 3.407 mm, right sphenoid floor 3.245 mm, and sphenoid roof 2.247 mm. There are statistically significant differences ($p < 0.05$) in bone thickness at nearly all sites along the sphenoid when comparing AERD to all control groups (Table 2; Figure 2). The most prominent differences in average

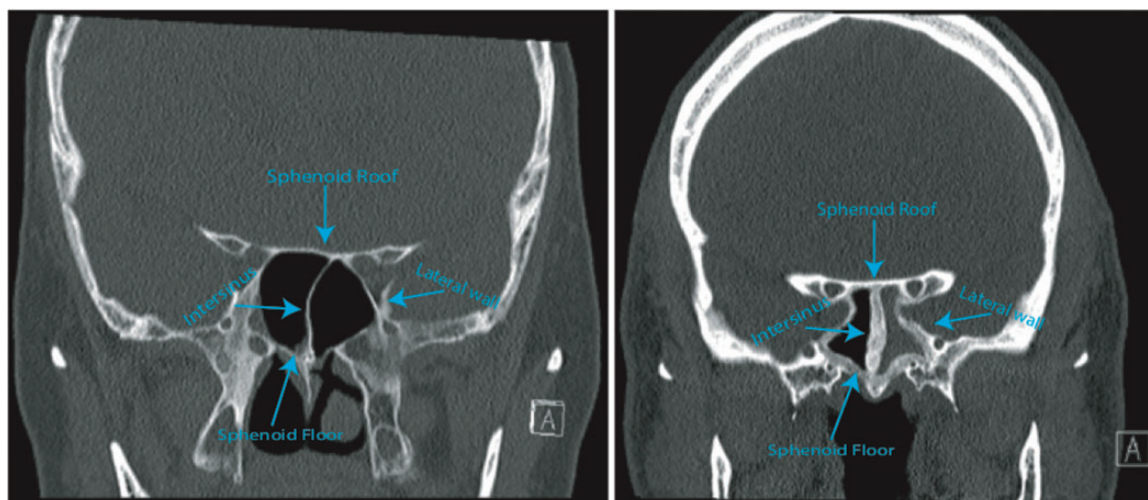


Figure 1. Representative CT scan used for measurements. Fine-cut coronal axial CT of the paranasal sinuses without contrast of a patient participant with AERD (right) compared to a patient without sinus disease (left). Images represent thickening of the four surrounding aspects of the sphenoid bone and the intersinus septum. Arrows identify areas of interest.

Table 1. Average Measurements (mm) of the Sphenoid Bone at Six Different Locations for Patients With AERD, Healthy, and Diseased Controls.

Disease State	N	Intersinus****	Left Lateral****	Right Lateral****	Right Floor**	Left Floor****	Sphenoid Roof ***
AERD	43	2.287 (1.894–2.681)	1.992 (1.721–2.263)	2.124 (1.831–2.418)	3.245 (2.807–3.684)	3.407 (3.074–3.740)	2.247 (1.793–2.700)
Healthy	22	0.8273 (0.715–0.940)	1.227 (1.080–1.374)	1.348 (1.085–1.611)	2.764 (2.181–3.346)	2.152 (1.675–2.629)	1.102 (0.965–1.239)
AFS	9	1.322 (0.756–1.888)	1.144 (0.688–1.601)	1.289 (0.824–1.754)	1.811 (1.145–2.477)	1.789 (1.082–2.496)	1.261 (0.826–1.696)
CRSwNP	18	1.214 (0.998–1.429)	1.475 (1.223–1.727)	1.397 (1.254–1.541)	2.294 (1.843–2.746)	2.439 (1.875–3.003)	1.289 (1.137–1.441)
CRSsNP	23	0.9413 (0.854–1.029)	1.154 (0.986–1.323)	1.093 (0.976–1.211)	2.739 (2.278–3.201)	2.526 (2.094–2.958)	1.402 (0.927–1.878)

One-way ANOVA p-values represent the significance of the thickness measurements at particular locations for a given disease state. Averages shown with (95% confidence interval).

**** $p < 0.0001$; *** $p < 0.001$; ** $p < 0.01$.

N: patient sample size, CRSwNP: chronic rhinosinusitis with nasal polyposis, CRSsNP: chronic rhinosinusitis without nasal polyposis.

thickness were seen along the intersinus septum. In an effort to identify whether a specific subset of AERD patients had more severe disease we analyzed bony thicknesses at each of the aforementioned subsites with respect to number of surgeries performed via one-way ANOVA. We found that no subsites had statistically significant associations with regard to the number of surgical interventions (Figure 3). Table 3 highlights the average number of surgeries within each disease group with additional data on patient demography.

Discussion

AERD is defined by a sequentially occurring triad of asthma, nasal polyposis, and aspirin sensitivity.^{1,2}

To our knowledge there have been no specific reports of sphenoid sinus osteoneogenesis as part of disease progression. In our study population of AERD patients there was significant bony thickening of the intersinus septum, lateral sphenoid walls, the roof and the left and right floor of the sphenoid sinus compared to healthy and diseased controls ($p < 0.05$). A vast majority of sites were found to be statistically different from our control populations with the most pronounced changes found at the intersinus septum. While not represented in the tables, there were no significant differences in thickness between the other disease states when excluding AERD. This suggests that AERD could present with a relatively thickened bony disease. Additionally, we were interested in identifying a particular subset of AERD

Table 2. Statistical Analysis of Ordinary One-Way ANOVA Multiple Comparisons Demonstrating Difference in Thickness Between AERD and Other Disease States at Varying Locations.

AERD vs.	Intersinus	P-value, CI	Left Lateral	P-value, CI	Right Lateral	P-value, CI	Right Floor	P-value, CI	Left Floor	P-value, CI	Sphenoid Roof	P-value, CI
Healthy	<0.0001	(0.827–2.092)	0.0001	(0.283–1.246)	0.003	(0.264–1.289)	0.774	(–0.440 –1.403)	0.0002	(0.460–2.050)	0.0008	(0.349–1.940)
AFS	0.0231	(0.080–1.850)	0.005	(0.174–1.521)	0.012	(0.119–1.553)	0.019	(0.145–2.723)	0.0006	(0.506–2.730)	0.121	(–0.127–2.098)
CRS _w NP	0.0002	(0.396–1.751)	0.0492	(0.001–1.033)	0.003	(0.178–1.276)	0.0672	(–0.036–1.938)	0.0153	(0.117–1.819)	0.0172	(0.106–1.810)
CRS _s NP	<0.0001	(0.723–1.969)	<0.0001	(0.363–1.312)	<0.0001	(0.526–1.536)	0.703	(–0.402–1.415)	0.0171	(0.0974–1.664)	0.0261	(0.0604–1.628)

CI: 95% confidence intervals.

CRS_wNP: chronic rhinosinusitis with nasal polyposis, CRS_sNP: chronic rhinosinusitis without nasal polyposis.

patients with more severe disease. We used number of surgical interventions as a surrogate for disease severity across the AERD group to the various aforementioned subsites. We found no significant difference of bony thickness for AERD patients across various levels of disease severity. However, this is an evolving area and a larger dataset could elicit a clearer answer to this question.

The osteogenic changes of CRS and AFS reflect two differing spectrums of disease and their effect on the sinuses. CRS is described as chronic paranasal sinus inflammation with the potential for underlying, irreversible bony changes in recalcitrant disease.⁷ The periosteal thickening described in CRS is histologically distinct from osteitis and osteomyelitis as there is absence of inflammatory infiltrates into the bone.^{7,8} The “neo-osteogenic” changes are potentially underlined by osteoblast activity and new woven bone formation, possibly secondary to reactive processes led by IL-4, IL-13, and type 2 inflammation.⁷ However, a recent study by Wu et al. examined the effect of bone morphogenetic protein (BMP) dysregulation on osteitic changes in CRS and demonstrated that dysregulated bone turnover may be the underlying factor to the bone thickening.⁹ The presence and degree of osteitic thickening are significant as they correlate to more severe disease and create an unclear picture of prognostic outcomes following surgical intervention.^{7,9,10} The more severe disease form, CRS with polyps, is associated with greater neo-osteogenesis and is a correlate of disease severity as these patients exhibit higher Lund-MacKay CT scores.¹⁰ AFS is a derivative of CRS with polyps characterized by a Type I hypersensitivity reaction with the presence of eosinophilic mucin and fungi within the sinus.¹¹ The pathophysiology creating the bony changes is not well understood, but may be related to the Type I hypersensitivity and IgE-mediated inflammation.¹¹ Regardless, the bony changes are distinct from that of CRS and AERD as they are characterized by bone erosion with sinus opacification and expansion.¹¹

While AERD appears unique with respect to the bone thickness at the sphenoid compared to other disease states, the underlying pathophysiology of the osteoneogenesis is well defined. However, it is likely a byproduct of the long-term inflammatory burden within the sphenoid sinus or any of the aforementioned mechanisms related with CRS osteoneogenesis.

Secondary to the continued hyperleukotriemia, aspirin sensitive sinus disease is a recalcitrant form of CRS with nasal polyposis. Patients with AERD are likely to require more sinus surgeries and experience a more difficult disease course with greater dependence on corticosteroids for management.¹² Identifying patients with AERD related CRS earlier in the disease spectrum may allow for better control of the inflammatory

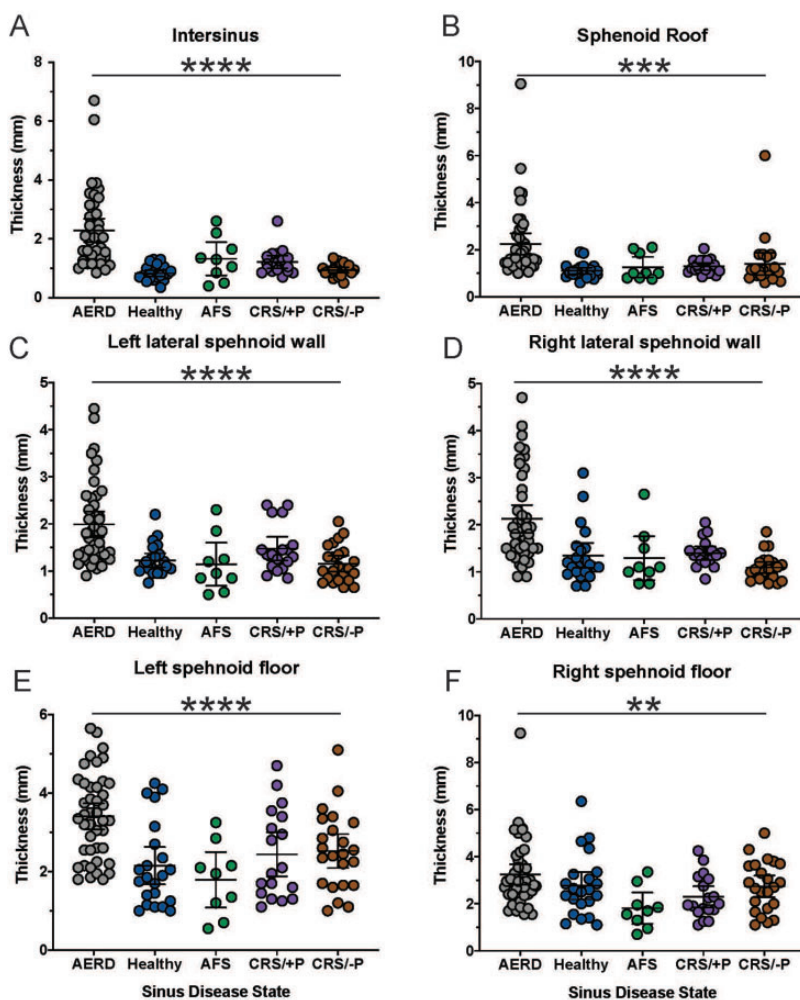


Figure 2. Measurements of sphenoid bone thickness between diseases states. Bone thickness (in mm) between AERD patients, healthy controls and other sinus disease states throughout the sphenoid cavity, including the intersinus (panel A), sphenoid roof (panel B), the bilateral lateral sphenoid walls (panels C, D) and the bilateral sphenoid floors (panel E, F). Error bars represent \pm SEM. Each dot represents the average of a single patient measurement (performed in duplicate).

**** $p < 0.0001$; *** $p < 0.001$; ** $p < 0.01$.

burden. Specifically, using bony changes within the sphenoid sinus could help clue clinicians into the possibility that aspirin sensitivity may be a contributing cause; however, at this time imaging is not required for diagnosis. The degree of bony changes within AERD exist on a spectrum. So, while many patients with AERD may have increased bone thickness, some will not show any significant osteoneogenesis. Diagnostic tools for AERD are evolving and increasing the diagnostic probability of defining imaging characteristics is an expanding area of interest. The bony changes in the sphenoid sinus in AERD could be a future reference point going forward.

The limitations of this study lie in its retrospective nature. There was no monitoring of the bony changes longitudinally; instead, we examined an isolated point in the patient's care and thus are unable to analyze the progressive changes associated with bony changes in

AERD. Additionally, we examined a heterogeneous patient population. Patients were recruited into the study at different times in their clinical course and there was no homogeneity in timing of operations, number of interventions, and medication regimen. Specifically, it would be beneficial to record the duration of disease and corticosteroid usage throughout the disease course; however, this information was not available for every patient in our analysis. We recognize these factors could play an important role in our current findings, but are unable to speculate on these clinical interventions and their effects on sphenoid sinus osteoneogenesis in our patient cohort.

Future studies will compare the bony changes in a prospective manner and also better establish the osteoneogenesis within the sphenoid sinus in different inflammatory states. The goal is to specifically compare

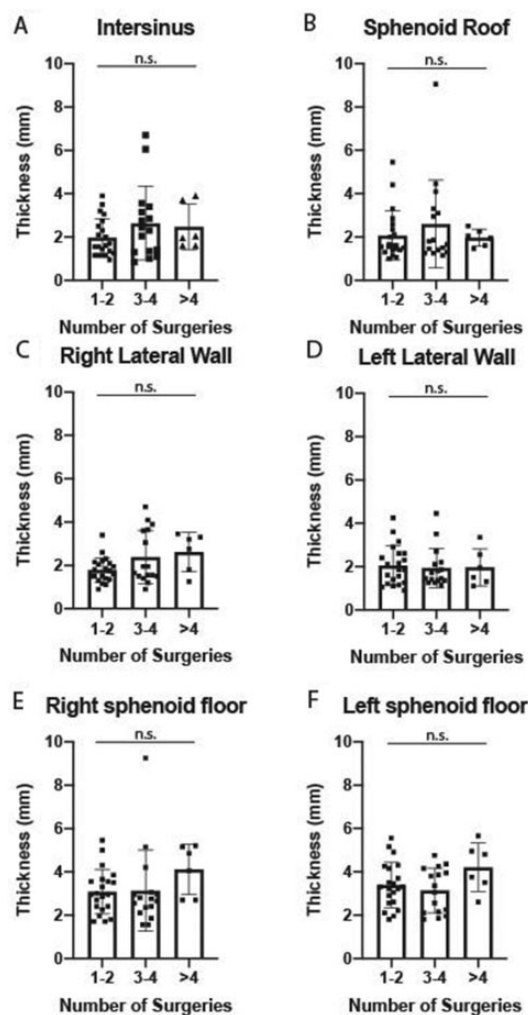


Figure 3. Bone thickness and disease severity within AERD. Bone thickness (in mm) of only AERD patients throughout the sphenoid cavity, including the intersinus (panel A), sphenoid roof (panel B), bilateral lateral sphenoid walls (panels C, D) and the bilateral sphenoid floors (panels E, F) grouped using number of functional endoscopic sinus surgeries as a surrogate for disease severity. Each dot represents the average of a single patient measurement (performed in duplicate). N.s: not significant ($p > 0.05$).

Table 3. Tabular Representation of Data Highlighting Demography and Comparison in the Average Number of Functional Endoscopic Sinus Surgeries Across Each Disease Group.

Disease State	Average Age (Years)	Sex	Average Number of Surgeries
Healthy	44.4 Range: 17–72	F: 16 M: 6	0.36
AERD	51.9 Range: 23–85	F: 23 M: 20	3.09

(continued)

Table 3. Continued.

Disease State	Average Age (Years)	Sex	Average Number of Surgeries
AFS	50.4 Range: 20–80	F: 4 M: 5	2.22
CRSwNP	49.6 Range: 29–73	F: 6 M: 12	1.28
CRSsNP	56.6 Range: 24–79	F: 13 M: 10	1.09

CRSwNP: chronic rhinosinusitis with nasal polyposis, CRSsNP: chronic rhinosinusitis without nasal polyposis.

variants of CRS including with and without nasal polyps and how the inflammatory profile of asthma, allergies, and aspirin sensitivity affect the sphenoid sinus.

Conclusion

There is a significant difference between the thickness of the sphenoid sinus bone in patients with AERD compared to both non-diseased and diseased controls. Further studies will focus on characterizing the pathophysiology behind this thickening and differentiating it from other osteitic changes present in various forms of CRS. Using osteoneogenesis as a diagnostic marker can help clue the clinician in to underlying aspirin sensitivity in CRS management.

Authors Note

Oral presentation at RhinoWorld, Chicago, IL, June 2019; Poster presentation at American Rhinologic Society, New Orleans, LA, September 2019.

Declaration of Conflicting Interests

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