Periostin and Inflammatory Disease: Implications for Chronic Rhinosinusitis

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Abstract

Objective. To provide a comprehensive overview of the emerging role of periostin, an extracellular matrix protein, as a key component in the development, diagnosis, and treatment of patients with chronic rhinosinusitis.

Data Sources. Medline database.

Review Methods. A state of the art review was performed targeting English-language studies investigating the role of periostin in cardiopulmonary, neoplastic, and inflammatory diseases, with emphasis on recent advances in the study of periostin in chronic rhinosinusitis.

Conclusions. Periostin has emerged as a novel biomarker and therapeutic target for numerous human pathologies, including cardiac, pulmonary, and neoplastic disease. The upregulation of periostin in chronic rhinosinusitis suggests the potential for similar roles among patients with sinonasal disease.

Implications for Practice. Chronic rhinosinusitis is a widespread disease with major clinical and societal impact. A critical limitation in the current treatment of patients with chronic rhinosinusitis is the absence of clinically relevant biomarkers to guide diagnosis and treatment selection. A review of the literature supports a likely role of periostin as a biomarker of chronic rhinosinusitis, as well as a novel therapeutic target in the future treatment of patients with sinonasal disease.

Keywords
periostin, biomarker, chronic rhinosinusitis, evidence-based medicine, review

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Periostin is an extracellular matrix protein critical to remodeling in organ development and inflammatory diseases, with a potentially pathogenic role in chronic rhinosinusitis (CRS). Periostin has been implicated in the development of dentition, periosteum, and myocardium; the process of inflammation in pulmonary, esophageal, bone marrow, and renal tissue; and the pathogenesis of heart failure and cancer metastasis. Periostin is also recognized as a biomarker in asthma for disease progression and prediction of treatment response. The unified airway theory posits that common genetic and environmental factors exert similar effects on the epithelia of the upper and lower respiratory tracts, thereby drawing parallels between disease processes such as asthma and CRS. Although the extracellular matrix has historically received relatively little attention in consideration of CRS mechanisms, the work on mucosal immunity in asthma has prompted evaluation of this component as it relates to sinonasal disease.

A major limitation in the current management of CRS is the absence of a clinically relevant biomarker for diagnosis and treatment selection. Recent studies described upregulation of the periostin gene (POSTN) and its protein product among patients with CRS, supporting the potential clinical utility of periostin in this disease process. Herein, we review periostin in terms of its discovery and function; role in cardiopulmonary, neoplastic, and inflammatory diseases; emerging importance in CRS; and burgeoning potential as a biomarker and therapeutic target in CRS.

Methods

A state of the art review was performed targeting studies of periostin in cardiopulmonary, neoplastic, and inflammatory diseases, with an emphasis on most recent advances in the study of periostin in CRS. A literature search of this rapidly evolving topic was conducted on December 1, 2018, with PubMed to access the Medline database. Prospective, retrospective, and comparative studies were considered, as well
Discrimination of periostin among CRSwNP, allergic rhinitis, and olfactory dysfunction.26 Peripheral eosinophil counts, lower pulmonary function orders, including CRSwNP, allergic rhinitis, and olfactory dysfunction.27 Additionally, higher serum periostin levels were correlated with more rapid decline in pulmonary function tests among patients with asthma, despite inhaled steroid treatment.38 This finding suggests that periostin is predictive of disease course among patients with asthma.38 Much like CRS, asthma is a heterogeneous disease composed of various subtypes, also known as endotypes. Periostin appears to play a greater role in certain asthma endotypes than others and was found to be useful in defining asthma endotypes. Kim et al found that serum periostin levels were significantly higher among patients with aspirin-exacerbated respiratory disease (AERD) than aspirin-tolerant asthma, among patients with eosinophilic asthma than noneosinophilic asthma, and among patients with severe asthma than noneuse asthma.39 In severe asthma, serum periostin is the best predictor of sputum and airway tissue eosinophilia when matched against serum eosinophil levels, fractional exhaled nitric oxygen, and IgE.40 Thus, periostin has gained acceptance among pulmonologists as a biomarker for patients with asthma with elevated Th2 signaling, termed “Th2-high” asthma.37,41,42 These patients present with increased eosinophilic inflammation, exacerbated airway hyperresponsiveness, thicker basement membranes, and enhanced responsiveness to corticosteroid treatment.26,37 Furthermore, periostin levels predict clinical outcomes benefits to the diseased heart.34 Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) inhibit the renin-angiotensin pathway, a cascade known to upregulate periostin expression.34 These medications are widely prescribed in cardiac disease and are known to stabilize ejection fraction and reduce postmyocardial infarction mortality.35,36 Administration of an ARB (valsartan) reduced periostin levels and prevented pathologic remodeling in a rat model of diabetic cardiomyopathy.34 Similarly, reduced the increase in periostin caused by mechanical stretch in a rat model of myocardial infarction.30

Asthma. Paralleling the findings of periostin in cardiac disease, several studies suggested a role for periostin in lower airway remodeling in asthma. Deposition of periostin in thickened basement membranes among patients with asthma appears to contribute to the process of subepithelial fibrosis.21 This fibrosis was replicated in an ovalbumin-based murine model of asthma in response to IL-4 and IL-13, both of which induced secretion of periostin from lung fibroblasts.21 In IL-4 and IL-13 knockout mice, periostin deposition and subepithelial fibrosis were significantly reduced, suggesting that periostin may serve as the intermediary between Th2 cytokines and lower airway remodeling for those with asthma.21 Periostin levels correlate with pulmonary disease severity and inform prognosis. Matsusaka et al found that patients with asthma with higher serum periostin levels demonstrated a higher prevalence of aspirin intolerance, higher peripheral eosinophil counts, lower pulmonary function scores, and an increased incidence of concomitant nasal disorders, including CRSwNP, allergic rhinitis, and olfactory dysfunction.37 Additionally, higher serum periostin levels were correlated with more rapid decline in pulmonary function tests among patients with asthma, despite inhaled steroid treatment.38 This finding suggests that periostin is predictive of disease course among patients with asthma.38

Peripheral eosinophilic asthma than noneosinophilic asthma, and among patients with severe asthma than nonsevere asthma.39 In severe asthma, serum periostin is the best predictor of sputum and airway tissue eosinophilia when matched against serum eosinophil levels, fractional exhaled nitric oxygen, and IgE.40 Thus, periostin has gained acceptance among pulmonologists as a biomarker for patients with asthma with elevated Th2 signaling, termed “Th2-high” asthma.37,41,42 These patients present with increased eosinophilic inflammation, exacerbated airway hyperresponsiveness, thicker basement membranes, and enhanced responsiveness to corticosteroid treatment.26,37 Furthermore, periostin levels predict clinical

Discussion

Periostin Discovery and Function

Periostin was first isolated in 1993 as a secreted factor from a mouse osteoblast cell line and was originally termed osteoblast-specific factor 2.20 This 93.3-kDa protein was then identified in cortical bone peristeum and periodontal ligament of adult mice.4 The unique morphology of periostin allows for the creation and remodeling of an extracellular meshwork architecture and, in turn, connective tissue with adjustable biomechanics.21-24 As an extracellular matrix protein, periostin enables cell adhesion and maintains tissue structure.22,26 As a nonstructural activating protein, also known as a matricellular protein, it activates cells by binding to their surface receptors.21,26 Periostin-integrin interactions, for example, activate numerous cell signaling pathways.26 This dual functionality as an extracellular matrix protein and a matricellular protein enables periostin to play a key role in remodeling damaged tissue.26

Multiple factors have been found to stimulate periostin activity. Induction of periostin by T-helper type 2 (Th2) cytokines IL-13 and IL-4 was demonstrated in bronchial epithelial cells and lung fibroblasts in asthma.21 For patients with CRS with nasal polyposis (CRSwNP), Seshadri et al recently discovered that mRNA expression of periostin in sinonasal polyp tissue correlates significantly with IL-13 levels in that tissue.27 Factors involved in nonallergic inflammatory states, including TGF-β (transforming growth factor B) subtypes 1 through 4 and angiotensin II, were also shown to stimulate expression of periostin.15,26

Periostin in Nonsinonasal Disease

Cardiovascular Disease. In cardiac tissue, periostin plays roles in development1 and remodeling in response to insults, including myocardial infarction28 and heart failure.29 Following cardiac injury, periostin upregulation is associated with extracellular matrix deposition and fibrosis30 and appears to be a primary contributor to myocardial remodeling, rather than a secondary phenomenon.31 Although conflicting data suggest that periostin may play a protective32 or deleterious31 role in cardiac remodeling, therapeutic modulation in cardiac models suggested that periostin inhibition

as in vitro, animal, and human studies. Articles in languages other than English were excluded.

The initial computerized search was for articles that mapped to “periostin” and “sinus,” “sinus disease,” “sinusitis,” and “chronic rhinosinusitis.” These were collected and the full texts reviewed. Upon review of the 44 English-language articles that returned from this search, 8 did not relate specifically to periostin and CRS and thus were excluded. Of the remaining articles, 5 were not primary research but review articles. The remaining 31 studies were primary research with periostin findings relevant to CRS. Each of these 31 studies is included in this state of the art review and summarized in Supplemental Table S1 (available in the online version of the article).
response to anti-IL-13 antibodies (lebrikizumab)\(^{43}\) and anti-IgE antibodies (omalizumab) among patients with allergic asthma.\(^{44}\) Among patients with steroid-resistant asthma who have high levels of periostin, lebrikizumab was initially found to be effective in improving lung function through targeting an inducer of periostin.\(^{43}\) However, in follow-up phase III trials, lebrikizumab was not consistent in reducing asthma exacerbations among biomarker-high patients, although it did appear to block IL-13 effects with unclear clinical relevance.\(^{45}\)

**Cancer.** Periostin is secreted by numerous human tumors or their surrounding stromal cells and was linked to oncologic processes in many organ systems.\(^{46}\) Periostin modulates cell signaling pathways via interactions with surface receptors, thereby contributing to tumorigenesis via enhanced cell survival, cell invasion, angiogenesis, and ultimately metastasis.\(^{46-49}\) Increased levels of periostin were documented in a variety of human cancers, including lung, pancreatic, bladder, ovarian, colorectal, gastric, thyroid, esophageal, prostate, biliary, hepatocellular, renal cell, nasopharyngeal, melanoma, and osteosarcoma.\(^{49}\) Periostin has recently emerged as a marker for cancer prognosis and a target for anticancer therapies.\(^{49}\) Offering periostin as a putative metastatic marker in breast cancer, Vardaki et al found periostin levels to be elevated in breast cancer–derived exosomes secreted by metastatic cells.\(^{50}\) This finding was validated in a cohort with breast cancer with nodal metastasis as compared with those having localized disease.\(^{50}\) Additionally, periostin levels are graduated among patients with colorectal cancer, as those with more advanced-stage disease demonstrate higher concentration.\(^{46}\) Periostin expression appears to enhance metastatic potential of colorectal cancer by preventing apoptosis and by augmenting endothelial cell survival to enable angiogenesis.\(^{10}\) Exposing colorectal cancer cells to antiperiostin antibodies was shown to activate apoptosis and enhance the cytotoxic effects of chemotherapy.\(^{10}\)

**Periostin in CRS**

In 2008, Stankovic et al first described elevated periostin levels in the sinonasal tissues of patients with CRS.\(^{2}\) Genome-wide transcription studies demonstrated expression of the periostin gene to be markedly upregulated in nasal polyps as compared with normal sinus mucosa.\(^{2}\) This finding was confirmed by real-time quantitative reverse transcription polymerase chain reaction (PCR) and immunohistochemistry (IHC).\(^{2}\) In a subsequent study, Platt et al mapped the topographic distribution of periostin expression in the sinonasal cavity with PCR, IHC, and Western blot analysis to validate differential gene expression at the protein level.\(^{51}\) Periostin overexpression was found to be specific to polyp tissue among patients with CRSwNP. It was not overexpressed in adjacent nonpolyp mucosa from the septum, inferior turbinate, middle turbinate, or lateral nasal wall.

Some studies, however, suggested that periostin is also upregulated in nonpolyp tissue in CRS. In 2015, Miloński et al found elevated periostin mRNA expression in polyp tissue and nonpolyp sinonasal mucosa from patients with CRSwNP and nonpolyp sinonasal mucosa from patients with CRS without nasal polyposis (CRSsNP) relative to that of control patients without CRS.\(^{52}\) Daines et al used complementary DNA microarray analysis and PCR to show upregulation and overexpression of periostin in chronically inflamed ethmoid sinus mucosa of patients with CRSwNP and CRSsNP when compared with healthy-appearing nasal floor mucosa.\(^{18}\) Further localization of periostin expression was provided by Ishida et al, who employed IHC to analyze sinonasal mucosa and polyp tissue samples from patients with CRSwNP and those with allergic rhinitis.\(^{3}\) Positive staining for periostin was found in the basement membranes of patients with CRSwNP and those with allergic rhinitis, with significantly greater production of periostin in CRSwNP than allergic rhinitis \((P < .05)\) and with both these conditions having significantly greater periostin production than that of controls (patients undergoing a septoplasty without sinus disease, \(P < .05)\). The authors suggested that CRSwNP and allergic rhinitis are Th2-mediated inflammatory diseases associated with tissue remodeling.\(^{3}\) These findings indicate a possible role for periostin in polyp formation and in tissue remodeling in inflammatory sinonasal disorders beyond CRSwNP.

Periostin expression was associated with degree of sinonasal remodeling and with indices of severity in CRS. Shiono et al found that patients with CRSwNP with diffuse periostin expression throughout the lamina propria are more likely to demonstrate tissue remodeling with a thickened basement membrane as compared with patients whose periostin expression is restricted to the more superficial subepithelial layers.\(^{14}\) Ebenezer et al found that greater periostin expression was associated with increased basement membrane thickness and subepithelial fibrosis in sinonasal mucosal biopsies from patients undergoing surgery for CRS.\(^{16}\)

Other extracellular matrix proteins tested, including fibulin 1, fibronectin, and type IV collagen, did not demonstrate such associations, leading the authors to suggest periostin as a biomarker to identify patients undergoing sinonasal remodeling changes.\(^{16}\) Supporting the remodeling effect of periostin, in experimentation of nasal fibroblasts from control patients, Yang et al found that periostin induces activation of the Src/AKT/mTOR signaling pathway, thereby enabling tissue remodeling via differentiation of fibroblasts into myofibroblasts and expression of extracellular matrix components.\(^{53}\) They further found that these periostin-induced effects are inhibited by glucocorticoid treatment (dexamethasone or fluticasone).\(^{53}\) Periostin has also been associated with CRS disease severity as gauged by radiographic analysis. Kim et al found higher levels of periostin in polyp tissue to be associated with higher Lund-Mackay computed tomography (CT) scores among patients with eosinophilic CRSwNP.\(^{54}\) Kimura et al found that serum periostin levels among adults with comorbid sinusitis and asthma are positively correlated with severity of sinusitis based on Lund-Mackay CT scores regardless of smoking status.\(^{55}\)
Periostin appears to contribute to Th2-driven eosinophilic inflammation through multiple mechanisms. Several studies suggested a specific association between periostin and eosinophilic CRS.\textsuperscript{15,53,54,56-59} Polyps in which eosinophils compose >10% of the inflammatory cell population are known as eosinophilic polyps.\textsuperscript{54} These polyps have increased periostin mRNA and protein levels as compared with noneosinophilic polyps.\textsuperscript{54} Serum periostin and tissue periostin IHC staining scores correlate with blood eosinophil proportion (\(P = .005\) and \(P = .024\), respectively) among patients with CRS.\textsuperscript{60} and serum periostin is positively correlated with tissue eosinophil infiltration among patients with CRSwNP.\textsuperscript{61} Periostin protein expression is increased with other allergic inflammatory factors and eosinophilic-associated proteins in nasal polyp tissue in eosinophilic CRSwNP (fold change, 3.95; \(P < .001\)).\textsuperscript{58,62} Furthermore, Kim et al found that periostin mRNA is upregulated in the nasal tissue of patients with moderate and severe eosinophilic CRS as compared with those with noneosinophilic CRS and control patients (\(P < .05\)).\textsuperscript{57} The authors posited that the varying courses of patients with CRS undergoing medical and surgical treatments likely reflect extreme diversity of immunologic endotypes that together compose CRS.\textsuperscript{57} Xu et al found that when in vitro eosinophilic nasal polyp fibroblasts are stimulated by upregulation of periostin, they increase expression of the growth factor VEGF (vascular endothelial growth factor) and the chemokines eotaxin 2 and RANTES (regulated on activation, normal T cell expressed and secreted, also known as CCL5).\textsuperscript{56} The authors interpreted their findings to suggest that periostin might contribute to the occurrence and progression of eosinophilic nasal polyps.\textsuperscript{56} Kim et al found that IgE stimulation of a cultured human mast cell line (LAD2 mast cells) induces production of periostin that, via integrin binding, activates epithelial cells to secrete thymic stromal lymphopoietin, in turn activating mast cells to produce IL-5.\textsuperscript{54} In support of these in vitro findings, Wang et al found that tissue periostin expression by immunoassay is significantly higher among patients with CRSwNP with high levels of IL-5 than among patients with low levels of IL-5.\textsuperscript{15} Gevaert et al used an ex vivo human mucosal model from nasal polyp tissue to show that higher tissue levels of IL-5 and periostin were associated with increased formation of extracellular eosinophilic tracts,\textsuperscript{63} which bind and kill bacteria such as \textit{Staphylococcus aureus},\textsuperscript{64} thereby contributing to antibacterial defense.

Analogous to the cardiac and asthma literature, controversy exists for whether periostin plays a protective role in some aspects of CRS pathophysiology. In a murine model of eosinophilic CRSwNP, Kim et al found that periostin knockout mice that received stimulation with \textit{S aureus} enterotoxin B demonstrated enhanced polyp-like lesion formation and increased mast cell infiltration relative to wild-type mice that received a similar inoculation.\textsuperscript{65} The authors suggested that the complete absence of periostin may cause a system of “airway hyperresponsiveness” in terms of mast cell infiltration and polyp-like lesion formation when appropriately stimulated (eg, by \textit{S aureus} enterotoxin B).\textsuperscript{65} However, the loss of periostin in these mice did not affect eosinophilic infiltration or mucosal thickness, as one might expect, suggesting that further study is needed to clarify the unexpected findings in this study.\textsuperscript{65}

Intense eosinophilic inflammation also underlies allergic fungal rhinosinusitis (AFRS). Thus, it is not surprising that periostin levels in polypoid tissue from patients with AFRS were found to be significantly elevated as compared with sinonasal tissue from patients with CRSwNP and healthy controls.\textsuperscript{25} Furthermore, higher periostin levels are associated with radiographic indices of more severe soft tissue disease (Lund-Mackay score) and bony disease (CT bone erosion score) in AFRS.\textsuperscript{25} In interpreting their results, Laury et al offered a potential parallel between enhanced periostin levels seen in cardiac myocytes and fibroblasts under mechanical stretch and enhanced periostin levels in AFRS, as mechanical stretch was theorized as a possible cause for bone erosion and expansion in AFRS.\textsuperscript{25}

Study of allergic rhinitis showed that periostin is likely involved in remodeling the nasal cavity in pathologies other than CRS.\textsuperscript{3,66} In an ovalbumin-based murine model of allergic rhinitis undergoing prolonged allergen challenge, periostin knockout mice exhibit thinner subepithelial tissue and lower levels of type I collagen in nasal mucosa, fewer eosinophils, and lower nasal symptom scores relative to controls and allergic rhinitis mice with periostin intact.\textsuperscript{66} These findings suggest that periostin deficiency may decrease nasal remodeling and symptom burden in allergic rhinitis.

**Implications for Practice**

**Diagnostic Utility: Defining CRS Endotypes with Periostin**

Endotypes are biologically related subtypes of a disease caused by distinct pathophysiologic mechanisms.\textsuperscript{11} Like asthma, CRS demonstrates marked heterogeneity, with many biologic processes converging into recognizable disease categories.\textsuperscript{57} Recent work linked periostin levels to specific CRS endotypes. Maxfield et al found that the serum periostin levels of patients undergoing endoscopic sinus surgery were significantly higher among patients with CRSwNP as compared with those without polyps.\textsuperscript{17} The mean serum periostin level of patients with CRSwNP was 94.8 ng/mL (95% CI, 67.3-122.4), whereas the mean serum periostin level of patients with CRSsNP was 41.1 ng/mL (95% CI, 34.4-42.9). As a molecular marker, periostin level of patients with CRSsNP was 41.1 ng/mL (95% CI, 34.4-42.9). As a molecular marker, periostin appears to reflect underlying Th2 inflammation associated with polyp formation, eosinophilia, and asthma comorbidity.\textsuperscript{15} In light of such correlations, the authors suggested that high and low serum periostin levels (eg, >50 or <50 ng/mL) could potentially serve as an objective means of determining CRS based on endotyping,\textsuperscript{17} rather than utilizing the current phenotypic system of classifying CRS based on the presence or absence of polyps.\textsuperscript{68,69} Furthermore, Kim et al studied tissue samples from patients
with CRS with eosinophilic and noneosinophilic polyps and found that when a patient meets criteria for 3 of 4 delineated markers (ie, periostin, IL-5, interferon-γ, and the ratio of CT scores for ethmoid and maxillary sinuses), a diagnosis of noneosinophilic CRSwNP is suggested with 84% sensitivity and specificity. Xu et al found that serum periostin levels significantly differ between eosinophilic and noneosinophilic CRSwNP and that employing a serum periostin cutoff value of 83.41 ng/mL yields a sensitivity of 72.9% and a specificity of 60.9% for the diagnosis of eosinophilic CRSwNP. As much as the pulmonary literature has reported utility for periostin as a biomarker for endotyping airway disease, the association of different levels of periostin with different CRS endotypes suggests the potential diagnostic utility that periostin offers for CRS.

Periostin levels may be assessed by blood draws for serum, biopsies of sinonasal tissue, epithelial brushing of mucosa/mucus, nasal secretions (collected on Merocels allowed to dwell in the nasal cavity), and samples of exhaled breath condensate. It was posited that periostin may move easily from inflamed tissue into nearby blood vessels; thus, serum periostin levels may readily reflect local production in inflamed tissue. In support of this concept, the basal level of periostin was found to be relatively low in serum (approximately 50 ng/mL) in comparison with other extracellular proteins (eg, fibronectin or vitronectin in the range of 200-300 μg/mL), rendering an increase in periostin from local production more readily discernible in serum versus these other proteins.

The ability to measure periostin in serum suggests potential for an eventual blood test for CRS; however, a consensus cutoff range for elevated periostin has yet to be determined. In an effort to establish reference ranges for serum periostin in an adult population, Caswell-Smith et al evaluated serum periostin levels among adults without asthma or chronic obstructive pulmonary disease, and they found a mean serum periostin level of 51.2 ng/mL (SD, 11.9; 90% confidence limits, 35.0 and 71.1), without any associations between logarithm periostin and age or sex. The breadth of this range suggests that there is some variation in “normal” periostin levels among individuals. Interestingly, the average serum periostin level in the control group in the study by Maxfield et al (38.7 ng/mL) falls toward the lower end of this range. It is possible that the control group in the study by Maxfield et al could represent a relatively healthier population than average with a lighter burden of comorbidities, which could influence serum periostin levels.

Jonstam et al performed receiver operating characteristic analyses to identify a cutoff value for serum periostin level to predict expression of IL-5 in nasal polyp tissue to identify patients with CRSwNP with moderate to severe Th2 inflammation. Similar to the cutoff value of 50 ng/mL recommended by Maxfield et al, Jonstam et al found that a value of 48.5 ng/mL offered the best cutoff for serum periostin level to predict the presence of IL-5 in tissue with 93.5% sensitivity and 62.5% specificity. The authors suggested that serum biomarkers such as periostin may be useful to predict the type of inflammation in sinonasal tissue in the absence of any invasive procedure such as a tissue biopsy.

**Periostin among Patients with CRS and Comorbid Asthma.**

Periostin levels appear to have a particularly strong link to CRS severity among patients with asthma. Kim et al found that serum periostin levels were higher among patients with AERD with comorbid severe CRS than among patients with AERD with less severe CRS, based on CT stage. Similarly, Asano et al found that serum periostin levels were higher among patients with asthma who had CRS than among those without CRS (109.6 ± 47.4 vs 83.2 ± 22.9 ng/mL). Out of all tested markers (ie, blood eosinophil percentage, serum total IgE, serum periostin, serum eotaxin, fractional exhaled nitric oxide, and sputum eosinophil percentage), serum periostin was the only biomarker that significantly correlated with Lund-Mackay CT score among patients with asthma and CRS and the only biomarker that offered reliable detection of nasal polyps among patients with asthma and CRS. Ninomiya et al found that serum periostin levels among patients with CRSwNP and asthma are significantly higher (125.5 ng/mL; range, 48-369) than that of patients with CRSwNP without asthma (101 ng/mL; range, 28-325; P < .001).

Wardzyńska et al detected periostin in exhaled breath condensate of patients with asthma and controls. Periostin levels in exhaled breath condensate were not associated with asthma severity, but they were significantly higher among patients with asthma with symptomatic CRS versus those without. Although their data suggest a significant influence of symptomatic CRS on periostin levels in exhaled breath condensate, it is not known from the data presented whether patients with CRS without asthma have similarly elevated periostin levels in exhaled breath condensate.

**Periostin in the Prognosis and Assessment of Therapeutic Response in CRS**

The goal of personalized medicine is to deliver the most effective treatment for individual patients based on their genetic disposition and the molecular basis of their disease. Associations of periostin with prognosis and treatment response for asthma suggest the same potential value of periostin among patients who suffer from CRS. In regard to medical therapy, De Schryver et al tracked periostin levels among patients with CRSwNP following systemic treatment for CRS. They found that methylprednisolone treatment (a 20-day course) reduced serum periostin levels at 4-week follow-up and that omalizumab treatment (injected every 2-4 weeks) reduced serum periostin levels at 8-week follow-up. The authors interpreted their findings as reflecting these treatments’ suppression of the eosinophilic inflammatory cascade in CRS.

In regard to surgical therapy, Ninomiya et al evaluated serum periostin levels among patients with CRSwNP with
regard to risk for postoperative recurrence, as defined by recurrence of nasal polyps or purulent drainage in the middle meatus >28 days after surgery. \(^\text{61}\) Receiver operating characteristics demonstrated that the serum periostin value of 115.5 ng/mL was the optimal cutoff point for postoperative recurrence, yielding a sensitivity of 60.7% and a specificity of 61.9% \((P < .01)\). \(^\text{61}\) The authors concluded that periostin protein expression in the serum of patients with CRSwNP is associated with postoperative recurrence of disease. \(^\text{61}\) Zhang et al demonstrated utility of periostin as a longitudinal biomarker for CRS disease burden treated with endoscopic sinus surgery. \(^\text{13}\) At the time of surgery and 3 months following surgery, patients with CRS underwent epithelial brushing from the frontal recess with disposable gastrointestinal cytology brushes. \(^\text{13}\) Based on periostin levels yielded by these epithelial brushings, elevated periostin levels among patients with CRS who underwent surgery decreased >3-fold by their follow-up visit 12 weeks after surgery. \(^\text{13}\) By that time, postoperative periostin levels among patients with CRS were comparable to that of control patients at the time of non-CRS surgery, possibly reflecting decreased local tissue remodeling after appropriate surgical intervention. \(^\text{13}\) The elevation of periostin in the diseased state and its subsequent resolution following therapy for CRS support the potential role for periostin as a biomarker for disease burden and responsiveness to treatment. \(^\text{13}\)

**Periostin as a Novel Target for Disease Control in CRS**

Periostin may not only be a biomarker for disease and treatment effect but may also serve as a novel therapeutic target for medical treatment of selected patients. \(^\text{67,79}\) Polyp regrowth occurs in 17% to 89% of patients with CRSwNP despite aggressive treatment, including surgery. \(^\text{40}\) A recent study by Brook et al demonstrated that revision sinus surgery among patients with CRSwNP and concurrent asthma was delayed by >2 years among patients who took an ACE inhibitor or ARB. \(^\text{67}\) It was hypothesized that this association may occur through suppression of periostin. \(^\text{67}\) ACE inhibitors and ARBs downregulate Th2 cytokines and inhibit expression of TGF-β and NF-κB, factors that were implicated in the pathogenesis of CRS and linked to periostin activity. \(^\text{81-83}\) Furthermore, antiperiostin neutralizing antibodies have been developed and used in cancer research, suggesting an alternative avenue for suppressing periostin in diseased states. \(^\text{10,84}\) Patients with CRS with high levels or periostin could perhaps benefit from systemic or topical periostin-targeted therapies.

**Periostin: Future Directions**

Continued advancement in rhinology hinges on identification of clinically applicable biomarkers. Periostin was demonstrated to be a clinically relevant biomarker for several nonrhinologic diseases and appears to be a likely candidate to serve a similar role for patients with CRS. To validate periostin as a clinically relevant biomarker for endotypes of CRS, study is needed of prospective cohorts of patients with CRS, representing diverse endotypes and associated comorbidities. Recruiting such cohorts will allow assessment of the relevance of periostin levels to the clinical outcomes of patients with CRS who undergo medical and surgical treatments, in terms of disease-specific and general health-related quality of life.

**Conclusion**

CRS has proved a challenging disease for physicians and patients alike with major clinical and societal impact. A critical limitation in the current management of CRS is the absence of clinically relevant biomarkers to aid diagnosis, inform prognosis, and guide selection and development of therapeutic options. Periostin is an extracellular matrix and matricellular protein implicated in tissue remodeling that was found to be a clinically useful biomarker among patients with asthma. \(^\text{11}\) In the CRS literature, periostin has emerged as a potentially powerful biomarker for disease and a novel target for future therapeutics.

**Author Contributions**

Ashton E. Lehmann, interpreting literature reviewed, drafting manuscript, revising manuscript, giving final approval, agreeing to be accountable for all aspects of the work; George A. Scangas, interpreting literature reviewed, critically revising manuscript, giving final approval, agreeing to be accountable for all aspects of the work; Regan W. Bergmark, interpreting literature reviewed, critically revising manuscript, giving final approval, agreeing to be accountable for all aspects of the work; Edward El Rassi, interpreting literature reviewed, critically revising manuscript, giving final approval, agreeing to be accountable for all aspects of the work; Konstantina M. Stankovic, interpreting literature reviewed, critically revising manuscript, giving final approval, agreeing to be accountable for all aspects of the work; and Ralph Metson, conception of manuscript, interpreting literature reviewed, critically revising manuscript, giving final approval, agreeing to be accountable for all aspects of the work.

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**References**


