The diagnostic importance of periostin as a biomarker in chronic rhinosinusitis with nasal polyp

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Abstract

Purpose The current studies in the literature report that periostin contributes to the formation of nasal polyps and may be a molecular biomarker for chronic rhinosinusitis with nasal polyps (CRSwNP). This study aims to investigate the effect of periostin in determining polyp burden in CRSwNP patients and evaluate its impact on postoperative surgical results and its functionality as a biomarker.

Methods The study included 26 patients who underwent endoscopic sinus surgery due to CRSwNP and 30 patients who were scheduled to undergo septoplasty due to isolated nasal septum deviation. We performed preoperative Lund–Mackay scoring and preoperative and postoperative SNOT-22 and Modified Lund–Kennedy scoring for the patients. Tissue and serum samples were collected from all patients in surgery and another serum sample was taken from CRSwNP patients at postoperative month 6.

Results Tissue eosinophil (p < 0.001), preoperative serum (p < 0.001), and tissue (p = 0.002) periostin were significantly higher in the CRSwNP group. We observed a statistically significant positive correlation between tissue eosinophil values and tissue periostin values in CRSwNP patients (p = 0.004). We found a statistically significant positive correlation between the tissue periostin values and postoperative SNOT-22 scores of the CRSwNP group patients (p = 0.005).

Conclusion According to the results of our study, we think that periostin can be used as a biomarker in the prediction, determination of disease severity, and prognosis of CRSwNP. Comprehensive cohort studies with larger patient series are needed to provide more information on the role and effects of periostin in cases of CRSwNP undergoing surgical treatment.

Keywords Biomarkers · Nasal polyps · Nasal surgical procedure · Periostin · Sinusitis
Introduction

Associated with high morbidity, CRSwNP is a chronic inflammatory disease that affects 1–4% of the general population and 25–30% of patients with chronic rhinosinusitis (CRS) [1]. The underlying mechanisms contributing to chronic sinonasal inflammation in CRSwNP have not yet been fully defined [2]. Nasal polyps (NP) are known to be associated with the activation of the T helper 2 (Th2) immune response, in which interleukin 4 (IL-4), IL-5, and IL-13 play a role in the formation [3]. Better identification of endotypes will ensure patient-based treatment plans and improved treatment results [4]. Biomarkers to be used for this purpose will provide critical information for endotyping and allow better identification of Th2 inflammation [5]. In the literature, various variables such as IgE levels, eosinophil and basophil percentages, basophil-to-lymphocyte-ratio, neutrophil-to-lymphocyte ratio, and eosinophil-to-lymphocyte ratio in blood and nasal tissue were associated with CRSwNP relapse [6]. The European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS 2020) reported that periostin is among the main biomarkers used to identify CRSwNP, the type 2 disease endotype of primary diffuse (bilateral) CRS [4]. Periostin is an extracellular matrix protein secreted by fibroblasts. It is involved in Th2-mediated allergic inflammation, tissue remodeling, and fibrosis formation, which are induced by interleukin (IL)-4 and IL-13 [3]. It accelerates eosinophil activation and plays a role in the maintenance of eosinophil-mediated inflammation [7]. Periostin, which has been shown to be a molecular biomarker for CRSwNP [3], has been reported to be associated with postoperative recurrence [8, 9]. In the recent studies, it has been stated that CT scores can be used to determine the prognosis of CRSwNP and to define its phenotypes and endotypes. Preoperative CT can be used for surgical planning, as well as for follow-up and postoperative treatment [10]. Moreover, some studies positively correlate periostin with the severity of CRSwNP in radiological evaluations [11, 12].

Today, the researchers still explore the reasons why some individuals are predisposed to develop NP, some NP patients are unresponsive to medical treatment and present a higher rate of recurrence after surgery. Our study aims to determine periostin levels in CRSwNP patients, investigate its relationship with polyp burden, and evaluate its impact on postoperative surgical results and its functionality as a biomarker.

Materials and methods

Study sample

The study included 26 CRSwNP patients who underwent endoscopic sinus surgery (ESS) and 30 controls who were taken to surgery for isolated nasal septum deviation and turbinate reduction. We followed EPOS 2020 for diagnosis of CRSwNP and paranasal computed tomography (CT) scan [4]. Patients under 18 years of age, with autoimmune disease, immunodeficiency, ciliary dysfunction, fungal rhinosinusitis, inverted papilloma, antrochoanal polyp, sinonasal malignancy, and patients with a history of steroid use in the last 1 month were excluded from the study.

We inquired about the basic demographic data, allergic rhinitis, asthma, aspirin allergy, and previous ESS by taking a detailed medical history from the patients participating in the study. We evaluated the severity of the disease in preoperative paranasal sinus CT according to the radiological Lund Mackay staging system [13]. We performed the Turkish version of SNOT-22 [14] was administered to the patients in the CRSwNP group preoperatively and at the 6th month postoperatively, and their endoscopic nasal examinations were scored simultaneously according to the Modified Lund–Kennedy staging system [15].

The local ethics committee approval (24/10/2019–23/12) was obtained for the study, and a voluntary informed consent form was signed by all patients agreeing to participate in the study.

Tissue and serum sample collection

To perform the immunohistochemical examination, we took polyp tissue from CRSwNP patients who underwent ESS under general anesthesia, and inferior turbinate mucosal tissue from patients who underwent septoplasty and turbinate reduction. After taking the tissues, we washed them with physiological saline solution, placed them in 1.5 ml Eppendorf tubes, and stored them at −80 °C until the study stage. For biochemical evaluation, we took venous blood samples from the forearm in the morning in a fasting state, centrifuged them at 4000 rpm for 20 min, and serum samples stored them at −80 °C until the analysis.

Tissue homogenizer preparation

Following paraffin tissue follow-up, 4 μm-thick sections were cut from polyp and normal nasal mucosa samples and were stained with hematoxylin–eosin (HE) immunohistochemical (IHC) staining method. 8 μm-thick sections were cut from each block to be placed in Eppendorf tubes.
Sections were prepared for isolation by embedding in paraffin block. 1000 μl of xylene was added to the sample and it was centrifuged at 9000 rotation per minute (RPM) for 1 min. The supernatant was taken.

**Mucosal eosinophilia determination**

The pathology department cut 4 μm-thick sections from 26 polyp and 30 normal nasal mucosa samples after paraffin tissue follow-up, stained them with hematoxylin–eosin (HE) immunohistochemical staining method, counted eosinophils with ×40 magnification in 10 randomly selected areas under the light microscope (Fig. 1). Mucosal eosinophilia was defined as > 10 eosinophils/high power field (HPF) as suggested by EPOS 2020 [4].

**Periostin measurement**

Periostin measurement in serum and from tissue homogenizer prepared by the pathology department was performed in accordance with the instructions given by the manufacturer in the package insert by using the ‘Human Periostin ELISA KIT’ (Bioassay Technology Laboratory, Shanghai, China. Catalog number: E3226Hu) commercial kit based on the sandwich Enzyme-Linked Immunosorbent Assay (ELISA) method. Eti-max 3000 (DiaSorin, Italy) was used for measurement, and plates were evaluated by reading at 450 nm. Concentrations were calculated using a linear curve. The results were expressed as ng/ml. The analysis range is 0.5–150 ng/ml, and the sensitivity is 0.251 ng/ml. Precision is intra-assay CV < 8% and inter-assay CV <10%.

**Statistical analysis**

Descriptive statistics were presented as frequency and percentage for categorical variables, as mean ± standard deviation (SD) for normally distributed continuous variables, and with their median (min–max) values or non-normally distributed variables. The assumption of normality was checked using the Shapiro–Wilk test. The Pearson’s Chi-square test was employed to analyze the relationships between categorical variables. In the analysis of the difference between the measurement values of the two groups, the Mann–Whitney U test was used when it did not fit the normal distribution, and the Student’s t test when it did. The difference between preoperative and postoperative measurements was analyzed with the Wilcoxon Signed Rank test. ROC (Receiver-Operating Characteristic) analysis was performed to differentiate the patients according to their preoperative serum periostin and tissue periostin values and to determine the cutoff points while predicting the presence of sinusitis in patients, and the results were provided with the area under curve (AUC), cutoff points, sensitivity and specificity values. The Spearman’s correlation test was used to determine the correlation between continuous variables. All analyzes were performed with the IBM SPSS 23.0 package program (IBM Corp., Armonk, NY). p values less than 0.05 were considered statistically significant.

**Results**

**General characteristics and clinical findings of CRSwNP and control groups**

A total of 56 patients were included in the study, 26 in the CRSwNP group and 30 in the control group. 10 patients (38.5%) in the CRSwNP group had previous ESS, 23 patients (88.5%) allergic rhinitis, 9 patients (34.6%) asthma, and 4 patients (15.4%) aspirin allergies. The average radiological Lund Mackay score was 19.85 ± 4.02. Table 1 shows demographic characteristics of the CRSwNP and control group, tissue eosinophil, tissue periostin, and preoperative serum distributions.

Median postoperative serum periostin in the CRSwNP group patients was 17.02 ng/ml (min–max 10.23–169.51) and median preoperative serum periostin in the control group was 16.4 ng/ml (min–max 7.43–164.86). We determined that postoperative serum periostin values of the patients in the CRSwNP group decreased, not creating a significant difference with the preoperative serum periostin values of the control group (p = 0.379). Figure 2 demonstrates the distribution of the postoperative serum periostin values of the CRSwNP group and preoperative serum periostin values of the control group.

The preoperative and postoperative clinical changes of the CRSwNP group patients are compared in Table 2. We found a statistically significant positive correlation between the tissue eosinophil values and tissue periostin values of the CRSwNP group patients (p = 0.004) (Fig. 3).
**Relationship of Periostin with SNOT-22 and objective tests**

We found no statistically significant correlation between the preoperative and postoperative SNOT-22 scores and the SNOT-22 difference (postoperative–preoperative) variable and the radiological Lund Mackay score, preoperative and postoperative endoscopic score and endoscopic score differences (postoperative–preoperative) \( (p > 0.05) \). We determined a strong positive correlation between the radiological score and the preoperative endoscopic score \( (p < 0.001) \).

We found a statistically significant positive correlation between the tissue periostin values and postoperative SNOT-22 scores of the CRSwNP group patients \( (p = 0.005) \). Table 3 presents the results of correlation analysis for the measurement of the CRSwNP group patients’ tissue periostin and serum periostin at different times and other variables.

**ROC curve analysis**

Figure 4 shows the result of ROC analysis performed for the preoperative serum periostin and tissue periostin in determining rhinosinusitis in patients. The optimal cutoff point determined by the Youden index for the tissue periostin in the prediction of rhinosinusitis was > 8.995 \( (AUC = 0.743 \,[95\% CI 0.609–0.850; \, p < 0.001]\); sensitivity = 92.31%; specificity = 53.33%). Although we determined that preoperative serum periostin is a differential factor for sinusitis \( (AUC = 0.781 \,[95\% CI 0.650–0.880]; \, p < 0.001)\), we calculated sensitivity as 92.31% and specificity as 66.67% for the cutoff point > 16,826 determined by the Youden index.
When the differential performance of the tissue periostin and preoperative serum periostin were compared, no statistically significant difference was observed ($p=0.701$).

**Discussion**

CRS with nasal polyps is a heterogeneous disease characterized by different phenotypes or endotypes [16]. Ensuring an objective classification of CRS, molecular biomarkers used in CRS endotyping are also used to monitor treatment success and predict the severity and reoccurrence potential of the disease [3, 17]. EPOS 2020 mentions them as one of the biomarkers to be used to identify CRSwNP disease [4]. A study compiling and reviewing 31 articles in the available literature concluded that periostin has a role as a biomarker of CRS and may be a new therapeutic target in the treatment of patients in the future [18].

In their pilot study in 2008, which is the first in the literature on the relationship between CRSwNP and periostin so far, as is known, Stankovic et al. showed that the expression of the periostin gene increased significantly in the NP tissues of 20 CRSwNP patients compared to the normal sinus mucosa of 10 controls [19]. Maxfield et al. found in their study that the mean serum periostin level was 94.8 ng/ml in 33 CRSwNP patients, 41.1 ng/ml in 38 CRSsNP patients, and 38.7 ng/ml in 62 controls [3]. Qin et al. found the serum periostin and nasal mucosal IHC periostin staining score to be significantly higher in 37 CRS patients (25 CRSwNP; 12 CRSsNP) compared to 15 controls while periostin mRNA levels were similar in the three groups [20]. Milonski et al. determined that periostin mRNA levels were significantly higher in 63 patients with CRSwNP and 23 with CRSsNP compared to 18 controls [21]. Kim et al. found periostin mRNA and protein levels to have significantly increased in 47 CRSwNP patients compared to 10 CRSsNP patients and 10 controls [11]. In parallel with the literature, our study showed that the preoperative serum periostin ($p<0.001$) and tissue periostin ($p=0.002$) values of the CRSwNP group were significantly higher than the control group ($p<0.001$).

A couple of studies suggested a specific relationship between periostin and eosinophilic CRS [7, 11, 22]. Yu et al. reported that increased periostin expression contributes to the pathophysiology of eosinophilic CRS and that suppression of periostin may suppress eosinophilic inflammation [23]. Ninomiya et al. determined serum periostin to be positively associated with tissue eosinophil infiltration in CRSwNP patients [8]. Kim et al. reported higher periostin mRNA expression and protein levels in eosinophilic NPs compared to noneosinophilic NPs [11]. Qin et al. found that serum periostin values and tissue periostin IHC staining scores had a significant relationship with blood eosinophil ratio in CRSwNP patients [20]. In their study with 32 CRSwNP, 15 CRSsNP, and 7 controls, Imoto et al. reported a significant correlation between periostin mRNA

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**Table 3** Correlation between the measurement of the CRSwNP group patients’ tissue periostin and serum periostin and other variables

| Variables | Tissue periostin | Preoperative serum periostin | Postoperative serum periostin | Serum periostin difference |
|-----------|------------------|------------------------------|------------------------------|---------------------------|
| r         | p                | r                            | p                            | r                         | p                         |
| Radiological score | −0.297 0.141 | −0.165 0.420 | 0.051 0.803 | 0.168 0.413 |
| Preoperative endoscopic score | −0.063 0.760 | 0.024 0.908 | 0.234 0.249 |
| Postoperative endoscopic score | −0.117 0.568 | −0.219 0.283 | −0.076 0.712 |
| Endoscopic score difference (Postoperative–Preoperative) | 0.048 0.814 | 0.205 0.314 | 0.124 0.545 |
| Preoperative SNOT-22 | −0.089 0.664 | 0.034 0.869 | −0.014 0.947 |
| Postoperative SNOT-22 | 0.530 0.005 | −0.177 0.386 | 0.028 0.892 |
| SNOT-22 difference (Postoperative–Preoperative) | −0.317 0.115 | 0.093 0.650 | −0.038 0.853 |

Spearman’s correlation test
expression and tissue eosinophil count in polyp tissue [22]. Similar to the literature, our study found a statistically significant moderate positive correlation between tissue eosinophil values and tissue periostin values among the CRSwNP group patients ($p = 0.004$). Unlike the literature, we did not determine a significant relationship between serum periostin and tissue eosinophil in the CRSwNP group ($p > 0.05$).

Periostin is known to have a role in the pathogenesis of diseases such as asthma, allergic rhinitis and CRSwNP, aspirin intolerance [24]. In the study by Maxfield et al., 22 of 33 CRSwNP patients had asthma and 8 had aspirin intolerance. While asthma alone was found to be associated with periostin level, no significant correlation was determined between serum periostin and aspirin intolerance and previous ESS in 71 CRS (33 CRSwNP; 38 CRSsNP) patients [3]. Ninomiya et al. found serum periostin to be significantly higher in the asthma group [8]. Ishida et al. measured periostin significantly higher in 46 patients with allergic rhinitis, CRSwNP, and aspirin intolerance compared to the control group [25]. Wei et al. found that tissue periostin had a significant positive relationship with previous ESS and asthma in 63 CRSwNP patients [12]. Unlike the literature, our study detected no significant relationship between serum and tissue periostin and asthma in the CRSwNP group ($p > 0.05$). While the literature presents different results, we found that allergic rhinitis, aspirin intolerance, and previous ESS did not make a significant difference for serum and tissue periostin.

Many studies available in the literature showed that serum or tissue periostin and the radiological Lund–Mackay score in patients with CRSwNP and CRS (CRSwNP, CRSsNP) had a statistically significant correlation [11, 12, 26–28]. Considering the relationship between SNOT-22 and periostin, as a result of a 2-year follow-up with 66 CRSwNP patients, Mueller et al. found that the increase in periostin levels measured from nasal mucus and the worsened SNOT-22 score were significantly correlated in the treatment-resistant group [29]. Kanemitsu et al. determined no association between sputum periostin levels and SNOT-22 score in 56 CRS patients [30]. Contrary to the literature, our study did not find a statistically significant relationship between serum and tissue periostin and the radiological Lund–Mackay score in the CRSwNP group ($p > 0.05$). Although the literature provides different results, we did not find a significant correlation between serum periostin and SNOT-22 score ($p > 0.05$) while determining a statistically significant positive correlation between tissue periostin and postoperative SNOT-22 score ($p = 0.005$). According to our literature review, the relationship between periostin and preoperative endoscopic score has not yet been evaluated, and we did not observe a significant relationship between periostin and endoscopic Modified Lund–Kennedy score in our study ($p > 0.05$).

Studies in the literature reveal the relationship of different periostin levels with CRS endotypes and the benefit of periostin in the potential diagnosis of CRS [18]. Qin et al. reported that the ROC AUC for serum periostin level was 0.8 in the ROC curve analysis, and when the periostin concentration exceeds the threshold of 38.56 pg/ml, patients can be diagnosed with CRS with a specificity of 0.867 and a sensitivity of 0.811 [20]. Xu et al. found that serum periostin levels differed significantly among the eosinophilic and non-eosinophilic groups in CRSwNP patients and that using a serum periostin threshold of 83.41 ng/ml provided a specificity of 60.9% and a sensitivity of 72.9% for the diagnosis of eosinophilic CRSwNP [16]. Maxfield et al. argued that high and low serum periostin levels (> 50 ng/ml or > 50 ng/ml) could potentially be used as an objective parameter in determining the endotyping of CRS [3]. Jonstam et al. established that serum periostin at 48.5 ng/ml with a sensitivity of 93.5% and a specificity of 62.5% could be used to predict IL-5 expression in polyp tissue of patients with CRSwNP and suggested that periostin-like serum biomarkers could be beneficial in predicting the type of inflammation in sinonasal tissue without the need for any invasive procedures such as tissue biopsy [31]. In our study, as a result of the ROC analysis for preoperative serum periostin and tissue periostin in determining CRS, the optimal cutoff point for tissue periostin was > 8.995 ng/ml (specificity 53.33%; sensitivity 92.31%), and > 16.826 ng/ml (specificity 66.67%; sensitivity 92.31%) for preoperative serum periostin. When comparing the differential performance of tissue periostin and preoperative serum periostin, we observed no statistically significant difference ($p = 0.701$). Based on our current

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**Fig. 4** ROC analysis for preoperative serum periostin and tissue periostin in determining rhinosinusitis
findings, we believe that serum periostin is sufficient for the prediction of CRSwNP.

Periostin expression is known to increase in active CRS and decrease with successful medical and surgical treatment. It has been suggested that periostin follow-up may be useful in evaluating CRS patients’ response to treatment [8]. The relationship of periostin with the known prognosis and treatment response for asthma has been shown to be similar in CRS patients [18]. Evaluating the postoperative recurrence risk defined by purulent discharge or polyp in the middle meatus 28 days after surgery in CRSwNP patients who underwent ESS, Ninomiya et al. determined the serum periostin value of 115.5 ng/mL to be the most appropriate threshold for postoperative recurrence and concluded that serum periostin expression is associated with postoperative recurrence of the disease [8]. In their study with 12 CRS patients on whom they performed ESS, Zhang et al. obtained epithelial brush samples from the frontal recess during and 3 months after the surgery and reported that the periostin levels decreased 3 months after the surgery, creating no significant difference with the control group [9]. In a study by Kanemitsu et al., serum periostin levels did not decrease at month 12 in 7 CRS patients who experienced recurrence after ESS and the authors stated that NP recurrence could be reflected by the change in serum periostin levels after ESS [32]. As a result of their study with 338 CRS patients, of which 278 had CRSwNP, Oka et al. reported that serum IgG4 and periostin could be new biomarkers in predicting postoperative recurrence [33]. Wei et al. also found a significant correlation between tissue periostin and polyp recurrence after ESS [12]. In our study, which included ten patients who underwent revision ESS, we saw that the postoperative month six serum periostin values of the CRSwNP group patients decreased in a way that did not create a significant difference with the preoperative serum periostin values of the control group ($p = 0.379$).

In our study, it was observed that the postoperative serum periostin values of the patients in the CRSwNP group were quite close to the preoperative serum periostin values of the control group. The finding of a statistically significant positive correlation between tissue periostin and postoperative SNOT-22 scores confirms that those with high tissue periostin, which is considered a biomarker to increase disease severity, will have higher symptom scores at month 6 postoperatively, as expected. In our study, the ROC analysis performed to determine CRS with preoperative serum periostin and tissue periostin showed that there was no significant difference between distinguishing performances of the tissue periostin and preoperative serum periostin. We think that the serum periostin measurement is sufficient to predict CRSwNP without the need for an invasive biopsy procedure. A positive and significant correlation was found between the tissue periostin values and the tissue eosinophil values, which are known to be directly proportional to the severity of nasal polyposis disease and postoperative recurrence in patients in the CRSwNP group. With more comprehensive studies in this area, the role of periostin protein in the detection of disease prevalence and recurrence rates can be clarified.

Not being able to perform elective surgeries due to the COVID-19 pandemic or the unwillingness of patients to come to the hospital due to the pandemic prevented us from reaching the targeted number in the study and control groups. As this is a thesis work and the project period has expired, the study had to be completed.

**Conclusion**

Our study is a prospective study investigating the prognosis relationship of periostin with surgical treatment of CRSwNP. According to our results, we think that periostin can be used as a biomarker in the prediction and prognosis of CRSwNP, and in the light of these results, our research will contribute to the current literature. More comprehensive cohort studies on large patient groups are needed to better understand the role of periostin and CRSwNP.

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**Declarations**

**Conflict of interest** The authors report no declarations of interest.

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