

Effect of inhaled corticosteroids on serum periostin levels in adult patients with mild-moderate asthma

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ABSTRACT

Background: Periostin is an extracellular matrix protein, and its expression is upregulated in airway epithelial cells in patients with bronchial asthma. Periostin may be a key molecule linked to type 2 T-helper cell inflammation. Inhaled corticosteroids (ICS) may suppress periostin-induced asthmatic inflammation. This study estimated the serum periostin levels in patients with asthma and evaluated the effect of ICS on the levels of periostin, peak expiratory flow rate (PEFR), and quality of life (QOL).

Methods: The study design was prospective, open label, and observational. Forty adults with mild-to-moderate bronchial asthma started on ICS and matched healthy controls were enrolled. The patients were evaluated for their serum periostin, PEFR, and QOL by using asthma QOL questionnaire scores at baseline and after 4 weeks.

Results: The mean $\pm$ standard deviation (SD) serum periostin concentration in patients with asthma was 90.36 ± 19.81 ng/mL, which was significantly higher ($p < 0.01$) compared with healthy controls (31.88 ± 8.71 ng/mL). ICS treatment for 4 weeks reduced the mean $\pm$ SD serum periostin levels to 58.78 ± 14.53 ng/mL. The mean $\pm$ SD PEFR increased significantly, from 225.25 ± 60.79 L/min to 292.5 ± 59.18 L/min ($p < 0.01$), after 4 weeks. Similarly, the mean $\pm$ SD when using asthma QOL questionnaire scores significantly increased, from 40.7 ± 7.84 at baseline to 59.33 ± 11.0 on day 28 after ICS therapy ($p < 0.01$).

Conclusion: The serum periostin level, a marker of allergic inflammation and remodeling, increased in bronchial asthma and was reduced with ICS therapy. ICS improved QOL scores and PEFR in patients with asthma.

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Periostin is an extracellular matrix protein, and its expression is upregulated in airway epithelial cells and the subepithelial layer in patients with bronchial asthma.^{1,2} Moreover, the levels of periostin expression correlate with the thickness of the epithelial basement membrane.³ It may be a key molecule that links type 2 T-helper cells inflammation and remodeling in cells (bronchial smooth-muscle cells and fibroblasts), probably the most important action of inhaled corticosteroids (ICS) in suppressing asthmatic inflammation. Therefore, serum periostin can predict resistance or hyporesponsiveness to ICS therapy. In an attempt to further evaluate the immunopathologic roles of periostin and search for a new potential surrogate marker for bronchial asthma, we investigated the plasma concentrations of periostin in adult patients with bronchial asthma before and after ICS therapy.

METHODS

This prospective, open-label, observational study was conducted in the Department of Pharmacology and Medicine, Lady Hardinge Medical College, between December 2016 and March 2018, after approval from the institutional ethics committee for human research. Patients who presented to the outpatient medicine unit, diagnosed with asthma of mild-to moderate severity, ages 18–55 years, and started on ICS according to the guidelines by the GINA⁴ were included. Pregnant women and active smokers were excluded. Patients with severe asthma or any other coexistent active pulmonary infection, or who had taken corticosteroids in any form in the past 4 weeks were also excluded. In this pilot study, a convenient sample size of 40 patients and 40 healthy controls was taken. Written informed consent was taken from all the participants. Before initiation of ICS, the baseline serum level of periostin was measured in blood samples (3–5 mL) from each patient. The study is registered with Clinical Trials Registry–India (CTRI/2018/05/014189).

The asthma severity score, quality of life (QOL) by using the QOLtech Mini Asthma Quality of Life Questionnaire (Mini AQLQ; QOL Technologies, Bosham, West Sussex, U.K.)⁵ and peak expiratory flow rate (PEFR) were assessed for each patient. All the patients were also prescribed an inhaled bronchodilator to use

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when needed. Four weeks after starting ICS, the patients were evaluated again for their serum periostin, QOL, severity of symptoms, and PEFR. Venous blood samples (3–5 mL) taken from the participants were centrifuged at 5000 rpm for 10 minutes, and serum was separated within 2 hours of collection of the sample. Serum samples were stored at -20°C , until the estimation of the marker periostin by using a commercial enzyme-linked immunosorbent assay kit (human periostin ELISA kit; Sincere Biotech, Beijing, China). The aliquots were labeled with the name and patient identification code.

Statistical Analysis

Data were transformed, coded, and entered into an MS-Excel spreadsheet (version 14.3.9) (Microsoft Corp, Redmond, WA). The results are expressed as mean $\pm$ standard deviation (SD). The periostin levels in healthy subjects versus patients with asthma were compared by using the two-tailed unpaired Student's *t*-test. A change in the serum values of periostin before and after ICS was compared by using the two-tailed paired Student's *t*-test. A $p < 0.05$ was considered statistically significant.

RESULTS

The mean $\pm$ SD age of the recruited patients at the beginning of the study was 37.23 ± 10.38 years. Of the 40 patients, 30 were women (75%). Forty age- and sex-matched healthy volunteers were also enrolled for the study. All the patients and healthy controls completed the study, and there were no dropouts. The mean $\pm$ SD age of the controls at the beginning of the study was 38.18 ± 10.47 years. The mean $\pm$ SD body mass index of the patients and controls were 21.4 ± 3.1 kg/m² and 21.5 ± 3.5 kg/m², respectively. None of the patients had a history of smoking or alcohol addiction. Of the subjects enrolled in the study, 75% had mild asthma and 25% subjects had moderate asthma, and none had severe asthma according to the severity of asthma score calculated at the beginning of study.

The mean $\pm$ SD PEFR of the patients with bronchial asthma who experienced an exacerbation ($n = 40$) was found to be 225.25 ± 60.79 L/min at baseline and increased significantly, to 292.5 ± 59.18 L/min, after 4 weeks of ICS ($p < 0.01$). The mean $\pm$ SD Mini AQLQ score increased from a baseline of 40.7 ± 7.84 in the patients of bronchial asthma at their first visit, to 59.33 ± 11 on day 28, *i.e.*, after 4 weeks of ICS therapy. Thus, there was a significant improvement in QOL ($p < 0.01$, paired *t*-test). There was a significant difference between mean $\pm$ SD serum periostin levels of subjects with asthma (at day 0) and healthy controls when using the unpaired *t*-test. The mean $\pm$ SD baseline serum periostin level was 90.36 ± 19.81 ng/mL,

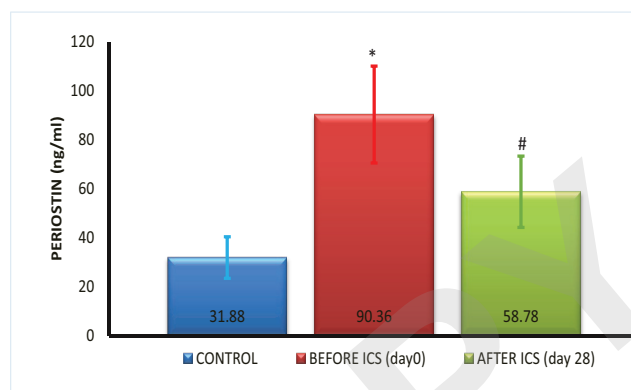


Figure 1. Serum periostin levels in healthy subjects (controls) ($n = 40$) and in subjects with bronchial asthma before and after inhaled corticosteroid (ICS) therapy ($n = 40$). Values are presented as mean $\pm$ standard deviation, compared by using two-tailed unpaired and paired *t*-tests. * $p < 0.01$, significant in comparison with controls; # $p < 0.01$, significant in comparison with before ICS therapy.

which significantly decreased to 58.78 ± 14.53 ng/mL after 4 weeks (Fig 1).

DISCUSSION

The primary objective of our research was to evaluate the effect of ICS on the serum periostin level in subjects with bronchial asthma. In our study, the mean serum periostin level in the patients with asthma was almost three times that of the healthy subjects. We also showed that ICS treatment in patients with asthma significantly reduced periostin levels after 4 weeks, but it was still higher than in the controls.

Matsumoto⁶ analyzed serum samples of healthy controls and of patients with bronchial asthma, and found that serum periostin levels of patients with asthma (average, 92.8 ng/mL) were significantly higher than the pooled serum periostin levels (average, 39.1 ng/mL) of the healthy subjects. In another study, with healthy adults, the periostin levels were found to be between 35.0 and 71.1 ng/mL (confidence interval-90%).⁷ Takahashi *et al.*⁸ showed that fixed airflow limitation was significantly associated with high serum periostin levels (≥ 97 ng/mL); the association was better than the fraction of exhaled nitric oxide, blood eosinophil counts, or total immunoglobulin E levels in the individuals with asthma. Our results were in agreement with a randomized controlled trial in which ICS significantly decreased the mean serum periostin level.⁹ The findings of improved QOL and PEFR with steroid therapy in patients with bronchial asthma were consistent with previous studies.^{10,11}

A major limitation of this study was the small sample size. Elucidation of the role of periostin in the inflammatory process requires the investigation of samples obtained from or near the site of inflammation, *e.g.*,

induced sputum, bronchoalveolar lavage fluid, or exhaled breath condensate, which was not done in the present study. Findings of our study should only be considered as preliminary because of the shorter duration of the follow-up and the small cohort size. For a better understanding about the role of periostin in bronchial asthma and the impact of ICS therapy on periostin, a longer follow-up study with a larger cohort size that involves both patients with acute bronchial asthma and patients with chronic bronchial asthma is required.

CONCLUSION

This study showed that serum periostin, a marker of allergic inflammation and remodeling, increased in bronchial asthma and reduced by ICS therapy. Whether serum periostin levels are a predictor of responsiveness to ICS therapy in patients with asthma needs to be investigated in a larger patient population.

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