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Circulatory Periostin levels as a Biomarker of Asthma Severity

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Abstract

Background: Asthma is a long-lasting inflammatory illness manifested as airway hyper-responsiveness induced by a series of inflammatory processes in the respiratory tract that can cause severe signs of an asthmatic attack. Periostin seems to subsidize numerous pathologic pathways in bronchial asthma, such as subepithelial fibrosis, eosinophil accumulations, and mucus overproduction from the goblet cells. This study intended to assess the plasma levels of periostin in bronchial asthma and its association with asthma severity. Methods: This was a case-control study, that included 163 asthma patients and 152 healthy control. The patients were diagnosed and supervised by the pulmonologists at Merjan Medical City hospital, Babylon, Iraq. in addition to serum levels of periostin, the study parameters included age, height, weight, gender, and family history, and the spirometric variables including FEV1, FVC, FEV1/FVC ratio, PEFR%, and the level of asthma control were evaluated depending upon GINA-guidelines. The serum levels of periostin were compared between asthma patients and the healthy control, using SPSS and a p-value < 0.05 as significant. Results: The mean ages of the studied members were 48.6 ± 5.9year, and 208 (65.6%) out of 317 were males. Serum periostin was significantly higher among the asthma group (P-0.05). the peak expiratory flow rate (PEFR) between asthmatic and control groups, which shows a significant difference (P-0.001). There was a significant difference in the distribution of periostin levels according to the severity of asthma based on the PEFR%, (P-0.001). Conclusion: The study concluded that measurements of serum periostin levels revealed a significant difference between asthmatic and healthy controls. Periostin levels were significantly increased with the severity of asthma based on the evaluation of PEFR%.

Keywords
asthma, inflammation, biomarkers, periostin, FEV1, FVC, PEFR%.

Asthma is a long-lasting inflammatory illness manifested as airway hyper-responsiveness to various stimuli that result in bronchial tree obstruction which is reversible by itself or by drugs (1-4). The series of inflammatory processes in the respiratory tract can cause severe signs of an asthmatic attack. Globally, 300 million individuals suffer from bronchial asthma and nearly 1000 persons die daily from asthma (4-6). The inflammatory reaction in asthma is very compound, containing a wide array of inflammatory body cells, comprising neutrophils, eosinophils, mast cells, and T- and B- lymphocytes that release a group of cytokines and mediators (1-4). These mediators control the reaction of other inflammatory modulators like C-reactive protein, a hepatic product with a well-known inflammatory role (4, 7-13). Additionally, these mediators have several effects causing narrowing of the airway smooth muscles, increasing vascular permeability leading to enhanced mucus secretion, and wall edema (14). The immunogens induce the release of interleukins (4 and 13) by specific immune cells, thus exciting eosinophils to periostin synthesis. Periostin is a protein that comprises 836 amino acids of 93.3 KD molecular weight and is also named osteoblast-specific factor 2 (Osf-2). The periostin turns on eosinophils (by autocrine pathway), to arouse their adhesion and also increase their enrolment into the airways of asthmatic subjects (6). Periostin seems to subsidize numerous pathologic pathways in bronchial asthma, such as subepithelial fibrosis, eosinophil accumulations, and mucus overproduction from the goblet cells (15).

It has been recognized that periostin is associated with several respiratory illnesses (16). In bronchial asthma, periostin works as a systemic marker of eosinophil-induced airway inflammation, due to its regulating ability of subepithelial fibrosis and mucus secretion. Hence, circulating levels of periostin are a valuable biomarker of response to therapy and/or disease progression (17). Developing shreds of evidence reveals elevated periostin levels in the respiratory airways of cases with “chronic obstructive pulmonary disease (COPD)” (18). Still, most revisions have concentrated on the protagonist of plasma periostin in the pathogenicity of bronchial asthma (19). Nationwide and worldwide recommendations acclaim the spirometry routine to identify and monitor bronchial asthma. It evaluates how much air one can breathe in and out. It furthermore assesses how rapidly the lungs can empty the air. As well, it gives a stronger validation of obstructive airways than the “peak expiratory flow rate (PEF)”, and therefore, is superior. A forced expiratory volume in 1 second over forced vital capacity (FEV1/FVC) ratio of less than 70% and FEV% below 80% approves obstructive airway disease (20).

This study aimed to assess the association of periostin plasma levels with asthma severity.

Patients and Methods

The present study included 317 subjects divided into two sets, the first included 165 patients on asthma treatment (whether they were on a regular inhaler, oral, injection treatment, or irregular occasional treatment) and without treatment, while the second group included 152 healthy control.

The patients' sample was recruited from those attending the outpatients’ respiratory clinic at Merjan Medical City, Hilla, Iraq. The patients were diagnosed and supervised by the pulmonologists at the hospital. Some tests were performed in the labs of the Department of Biochemistry in the Faculty of Medicine, University of Babylon.

Asthma was detected according to the GINA criteria (1, 2, 4, 20) on the origin of the proposed symptom and sign, spirometry (20), and chest x-ray. While the members' weight and height were calculated by electronic balance and measuring tape respectively. The index of body mass (BMI) was measured by weight (kg) divided by the squared height (m^2). Both height and weight of all the candidates were

measured by the same scale (5).

The demographic parameters include age, height, weight, gender, and family history, and the spirometric variables including FEV1, FVC, FEV1/FVC ratio, PEFR%, and the level of asthma control were evaluated depending upon GINA. A simple spirometer was used to confirm airflow limitation with a reduced FEV1 and FEV1/FVC ratio. The reversibility is verified by more than 12% and 200mL elevation of FEV1, 15 minutes after inhaling a short-acting β_2-agonist or in certain asthma patients after a 2-4 weeks trial of oral steroids (21).

Inclusion criteria

Any asthmatic patient as defined by the ''GINA-Guidelines", while healthy control included individuals who accepted to contribute to the present study.

Exclusion criteria

Any patient who suffered from one of the following was excluded from the study: < 6 years of age, smoking > 10 packs/year, interstitial lung diseases such as drug-induced pulmonary fibrosis, idiopathic pulmonary fibrosis, COPD, lung cancer, and bronchiectasis. In regard the periostin, the study excludes bone fracture, bone marrow fibrosis, blood hypertension, proven ischemic heart disease, proven heart failure, documented dyslipidemia patients, and documented cancer patients or on chemotherapy.

Periostin and spirometry analyses

Two milliliters of venous blood were obtained from a 5ml disposable syringe for the periostin test. The serum samples were kept at −20°C freezing till the testing time. The periostin plasma levels were tested at labs of the Department of Biochemistry, Faculty of Medicine at the University of Babylon using a human periostin ELISA kit from (PARS BIOCHEM, China). The pulmonary function tests including FEV1% and FEV1/FVC of all patients and the control were recorded twice using the spirometry available at the hospital.

Statistical analyses

The study data were expressed as means±SD, median, and interquartile percentages. Statistically, the significant variation was measured as a two-tailed $P<0.05$. The statistical analysis was executed using the SPSS package (IBM-USA) for Windows, V-22.

Result

This study is a case-control study performed in Merjan Teaching Hospital where the asthmatic group was 165 patients (65.6% females and 34.4% males) and the control group was 152 persons.

Distribution of basal study characteristics among asthmatic and control groups

Table-1 revealed basal characteristics of the study among asthmatic and control groups. No significant differences were observed regarding age, sex, and BMI between the two study groups. There were significant variations in the levels of PEFR% (less among the asthmatics p-0.05), and serum periostin was significantly higher among the asthma group. There was a strong family history of asthma among the asthma patients.

Table-1: Basal characteristics of the study among asthmatic and control groups

Characteristics		Total (N-317)	Asthmatics (N-165)	Control (N-152)	P-Value
Ages/years		48.6 ± 5.9	59.6 ± 13.1	49.3 ± 9.8	> 0.05
Sex	Males	208 (65.6%)	105 (63.6%)	103 (76.8%)	> 0.05
	Females	109 (34.4%)	60 (36.4%)	49 (32.2%)	
BMI (KG/m^2)		29.1 ± 6.9	28.5±7.4	31.2±8.8	> 0.05
PEFR%		71.1 ± 23.6	62.6±22.1	88.4±16.7	0.05
Periostin (pg/ml)		54.4 ± 9.1	58.2±8.1	46.3±3.5	0.05
Family history		129 (40.7)	116 (70.2%)	13 (8.6%)	0.05

Distribution of body mass index between the study groups

The study displayed significant variations in the distribution of BMI classes between patients and control groups (*P*-0.001) as shown in figure (1).

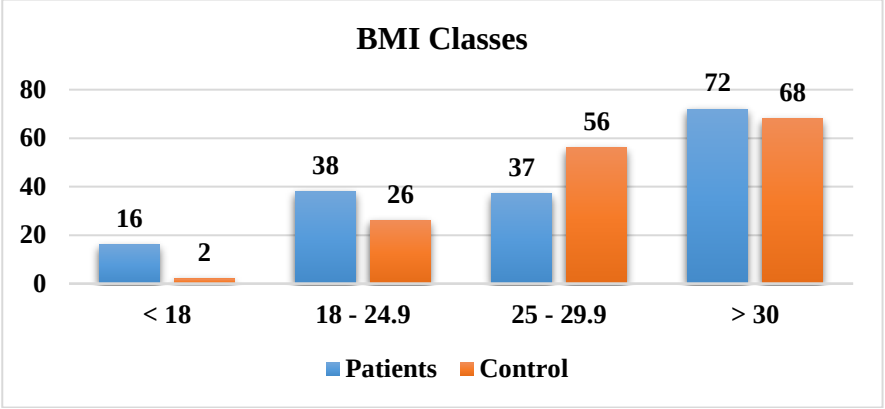

Figure (1): Distribution of classes of BMI between the study groups

Distribution of the classes of the peak expiratory flow rate (PEFR) between asthmatic and control groups

Figure-2 revealed the distribution of the classes of the peak expiratory flow rate (PEFR) between asthmatic and control groups, which shows a significant difference (*P*-0.000).

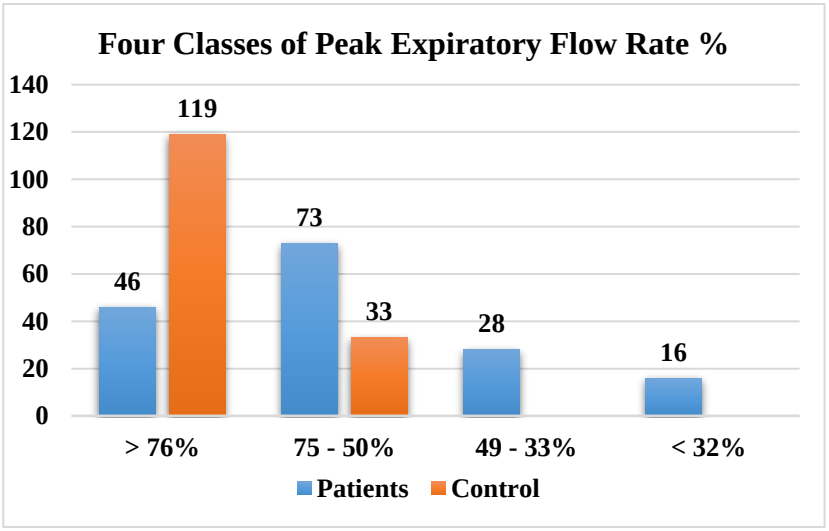

Figure (2): Distribution of classes of PEFR measures between the two study groups

Distribution of the serum levels of periostin between the groups

Significant differences were shown in the distribution of the measures of serum periostin level (pg/ml) between the study groups (P-0.001) as illustrated in figure-3.

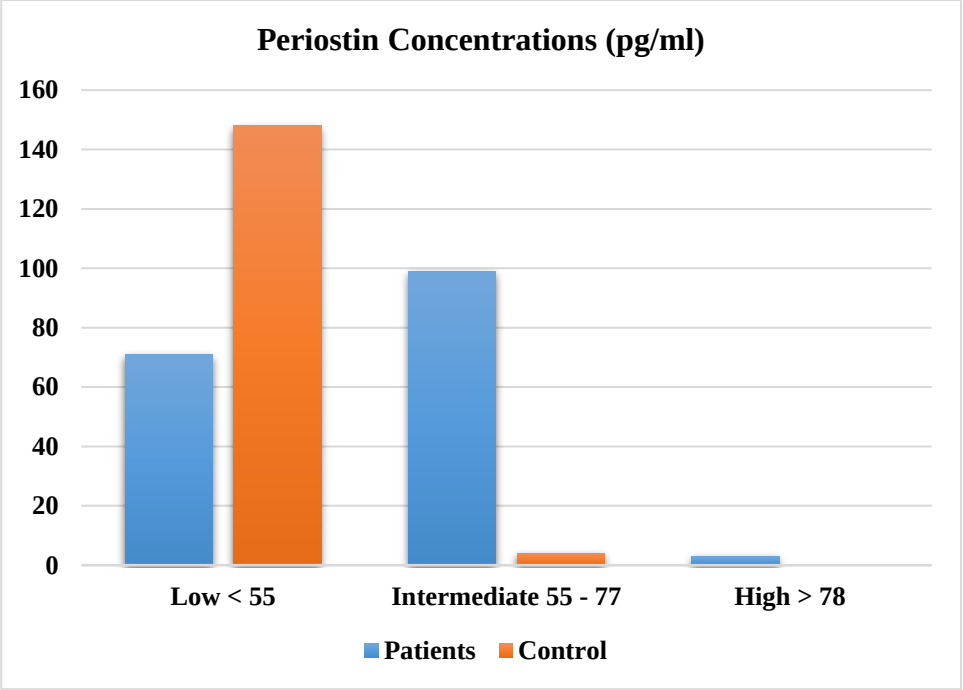

Figure (3): Distribution of the serum concentrations of periostin between the study groups

Distribution of blood periostin according to the asthma severity based on the PEFR%

A significant difference was exposed in the distribution of periostin levels concerning the severity of asthma based on the PEFR%, (*P*-0.001), figure 4.

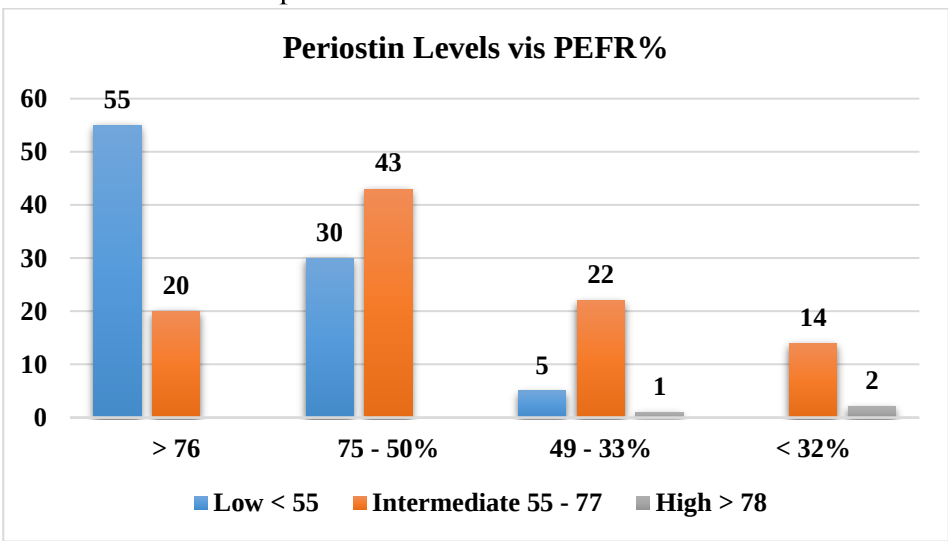

Figure (4): Distribution of periostin serum levels according to the severity of asthma based on PEFR%

Distribution of periostin serum level based on the BMI classes in asthmatic patients

A non-significant difference was presented in the distribution of serum periostin levels according to the BMI classes in the asthmatic group (*P*-0.6), figure-5.

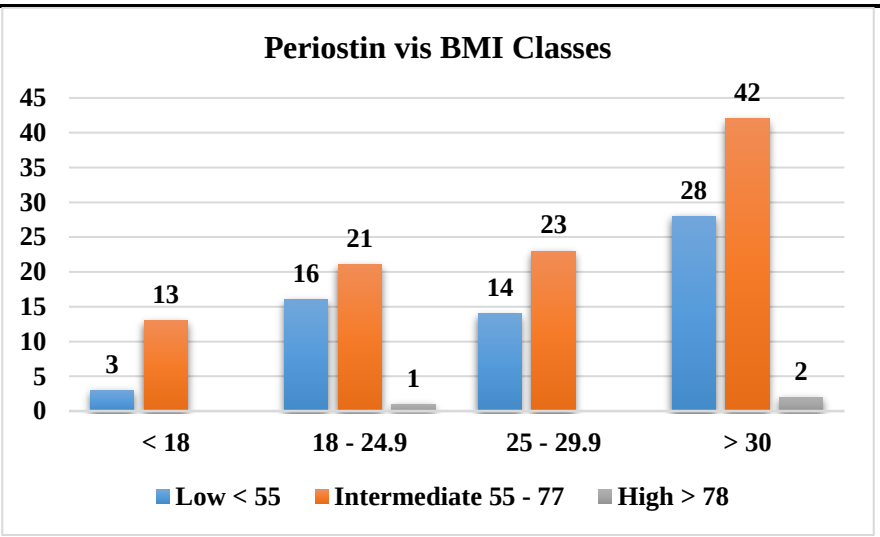

Figure (5): The relationship between periostin level (pg/ml) and BMI in asthmatic patients

Discussion

Asthma is a long-lasting inflammatory illness characterized by pathological airflow inflammation/remodeling. Physicians have to personalize the therapeutic regimes to avoid the progress or deterioration of respiratory airway remodeling (22).

In the current research, there is a significant difference in serum periostin (pg/ml) between the study groups (*P*-0.000). This finding was compatible with that of Jia *et al.* who reported that blood periostin measures among the asthma group were significantly high (23). Moreover, the present findings are compatible with Bentley *et al.* who observed that serum periostin was associated with the severity of airway hyperresponsiveness and immune responses in a murine model (24). Another study showed that periostin values in the sputum are related to the limitation of the airflow and with eosinophilic asthma phenotype even with high-dose of inhaled steroids (25).

Marwa E. et al. exposed that circulatory periostin measures were significantly raised in the eosinophilic asthma phenotype (26). A prior study exposed that peripheral periostin tests may perhaps be a predictor of asthma development among children. They found higher periostin levels among asthmatic children compared with non-asthmatic children (27). Meanwhile, other scholars revealed that periostin levels were considerably high in the serum of eosinophilic asthma patients (28).

Using markers to diagnose, predict asthma outcomes, and assess response to targeted regimes has a prodigious clinical implication, mainly in severe asthma. Recently, substantial research has been comprehended in the documentation of valid markers for bronchial asthma. Several pro-inflammatory biomarkers have been enrolled in asthma pathophysiology including C-reactive protein (4), interleukins (1, 2), tumor necrosis factor (29), and periostin (30).

The character of periostin in bronchial asthma and inflammatory response is a field of active research. Lately, evidence has shown that periostin defends mice from allergic inflammation of respiratory airways. Other studies exhibited that periostin enhances allergy-triggered eosinophil recruiting in the lung (31, 32). Periostin is contributed to several phases of asthma pathogenesis as well, like airway remodeling, and the progress of Th2 cells, and shares in the amplified expression of immunomodulators (33). The recent shreds of evidence propose that the initial periostin levels existing in the lungs are enough for the acute inflammatory response, and probably gathered amounts of periostin might augment or

sustain "Idiopathic pulmonary fibrosis" related inflammation (34).

Other evidence suggested that FEV1 acts as an independent predictor of exacerbations of bronchial asthma and children with a baseline FEV1 below 60% are expected to increase the risk for asthma exacerbation twofold in the consequent year in comparison to those with more than 80% of the predicted FEV1(35).

In the present study, there was a substantial difference in the distribution of periostin levels concerning asthma severity as measured by PEFR (*P*-0.000). This finding is consistent with other studies that reported that high plasma periostin levels (⩾95ng/ml) were the exceptional marker, among numerous biomarkers, linked with the higher yearly deterioration (minimum of 30ml/year) in FEV1 (23). Raised levels of periostin could recognize patients at risk of fast-declining FEV1 and asthmatic exacerbations even with high dosages of inhaled steroids (26). Asthmatic children with exercise-induced attacks with extreme declines in FEV1% after exercise were positively associated with blood periostin values (36). One study revealed higher periostin concentrations were considerably associated with a higher annual drop in FEV1% (37).

Additional well-designed, large population cohorts will further validate the outcomes of the study particularly if other pro-inflammatory mediators are evaluated to clarify the exact pathophysiology and cellular pathways of periostin in bronchial asthma patients.

Conclusion

The study concluded that measurements of serum periostin levels revealed significant differences between asthmatic patients and healthy subjects. Periostin levels were significantly increased with the severity of asthma based on the evaluation of PEFR%.

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