Correlation between serum periostin biomarker, spirometric airflow limitation, and airway dimensions by multidetector computed tomography in bronchial asthma

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Background Periostin has shown to be involved in the many aspects of allergic inflammation, such as acceleration of allergen-induced eosinophil recruitment, development of a Th2 phenotype, increased expression of inflammatory mediators, and airway remodeling and fibrosis in bronchial asthma and that fibrosis is one factor that causes steroid resistance or hyporesponsiveness in bronchial asthma.

Aim This study aimed to evaluate the possible role of serum periostin as a biomarker for airway inflammation, for predicting the patient's possible response to inhaled corticosteroids (ICS) after its regular use and its correlation with disease severity and control compared with functional and radiological findings.

Patients and methods Sixty nonsmoker, asthmatic patients of at least 20 years of age and 20 control healthy nonsmokers with matched age and sex were included. Patients were then subclassified into two: first, according to the asthma severity into mild, moderate, and severe and then according to asthma control (controlled, poorly controlled, and uncontrolled). Serum periostin, spirometry, and multidetector computed tomography were performed for all included populations.

Results There was significant statistical direct relation with increased serum periostin level and wall area and bronchial wall thickening (BWT) with asthma severity and all showed high significant increase among patients with uncontrolled than those with controlled asthma. Highly significant statistical direct correlation was found between BWT and serum periostin level. There was highly statistically significant decreased serum periostin level and BWT among the steroid-treated group of patients than in steroid-naive asthma (nonsteroid treated group of patients) which were significantly decreased after regular daily use of ICS for 6 months and also among uncontrolled patients after being adequately controlled than their baseline states.

Conclusion Serum periostin marker and BWT had a significant, sensitive, accurate clinically relevant indicative value (especially when combined) as regards asthma control and severity and probable adequate response to ICS. Serum periostin not only could be a reliable biomarker for eosinophilic inflammation but also may contribute to the development of airway remodeling as assessed by multidetector computed tomography.

Egypt J Bronchol 2018 12:160–172

Egyptian Journal of Bronchology 2018 12:160–172

Keywords: bronchial asthma, functional, multidetector computed tomography, periostin, serum

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Received 22 January 2018 **Accepted** 8 March 2018

Introduction

Approximately 300 million people have bronchial asthma worldwide and its burden is estimated to rise in the next few decades. About 20% of asthmatic patients have severe asthma, of which 20% is poorly controlled. Eosinophils are considered as the main cells involved in asthma-related airway inflammatory response. However, several inflammatory cells such as neutrophils, mast cells, and Th2 cells with numerous mediators such as interleukin (IL)-4, IL-5, and IL-13, play an important role in the development and persistence of eosinophilic inflammation and hyperresponsiveness in the asthmatic airways [1]. Persistent eosinophilic inflammation of asthmatic airways is the main stay process involved in irreversible airway obstruction. Owing to early diagnosis and intervention using inhaled corticosteroids (ICS), airway inflammation and remodeling that cause progressive annual decline in pulmonary function have been attenuated in most of asthmatics [2]. However, patients with severe asthma may remain refractory and their symptoms remain inadequately controlled despite receiving highest tolerable doses of ICS, long-acting bronchodilators, and leukotriene receptor antagonists. Although this has only been reported in a limited population of patients representing those with uncontrolled severe asthma and comprising only 5–10% of the total asthma population, structural and in turn functional consequences of airway remodeling and thickening account for nearly 50% of the total medical cost of treating and controlling patients with asthma, as they are at a high risk of frequent severe exacerbations, prolonged hospitalization, death, and have severely impaired the quality of life as well [3]. Anti-IgE monoclonal antibody is the recent developing and promising agent added to the list of treatment modalities for inadequately controlled asthmatics and has been suspected to reduce the frequency and severity of exacerbations along with emergency visits. It is also

suspected to play an important role in improving airway remodeling, symptoms, lung function, and in turn quality of life among patients with poorly controlled asthma. Biologics including IgE antibodies are recently developed effective antiasthma medications, but are very expensive. So, it is essential to classify asthmatic patients into subgroups according to their response to ICS or anti-IgE antibodies to ensure proper outcome [4]. Periostin, an extracellular matrix protein, was originally found as an osteoblast-specific factor that binds to collagen and fibronectin [5]. Moreover, serum periostin release is induced by IL-4 and IL-13, so is recently identified as the new serum marker predictor of airway eosinophilia, especially in patients with severe asthma who remain symptomatic and inadequately controlled despite using maximum doses of ICS treatment [2]. These patients present with increased eosinophilic inflammation and airway hyperresponsiveness, thickened basement membranes (periostin was found to stimulate and enhance profibrotic tumor growth factor-β deposition leading to subepithelial fibrosis which is one of the most important factors causing steroid resistance or hyporesponsiveness in bronchial asthma). So serum periostin is suspected to predict either resistance or hyporesponsiveness to ICS in patients with asthma [6]. Periostin expression by IL-13 is sensitive to corticosteroids and that expression of periostin is downregulated with corticosteroid treatment (its expression is reduced with ICS) in patients with bronchial asthma. Therefore, periostin is considered as a noninvasive new serum biomarker predicting Th2/eosinophil-mediated airway inflammation associated with functional decline; a consequence of airway thickening and remodeling, thus properly assessing treatment response in poorly controlled severe asthmatic patients. On the other hand; periostin is a biomarker which is not only used for diagnosis, but also for categorizing and subclassifying asthmatic patients according to their response to ICS. It is also called 'companion diagnostics' because it is used to predict the efficacy of antiasthmatic drugs [7]. So, the present study aimed to evaluate the possible role of serum periostin as a biomarker for airway inflammation, for predicting the patient's possible response to ICS after its regular use and its correlation with disease severity and control compared with functional and radiological findings [airway thickness and dimensions assessed by multidetector computed tomography (MDCT)].

Patients and methods

Patient selection

Inclusion criteria

This study was conducted between January 2013 and January 2016 at Chest Department, Faculty of Medicine, Ain Shams University Hospitals and Misr University for Science and Technology. A very large number of asthmatics were recruited and then they were selected and distributed equally in each group according to asthma severity for proper analysis and to avoid bias. So, several patients were excluded although fulfilling the inclusion criteria, but as a trial to equalize the included patients in each group. So 60 nonsmoker asthmatic patients of at least 20 years of age were referred from the outpatient clinic and 20 control healthy nonsmokers with no history of allergic diseases with matched age and sex were also included, with the following inclusion criteria for asthmatic patients:

(1) Prior physician's diagnosis of asthma.
(2) Low forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio, which is defined as less than 70% or below the fifth percentile in adults with reversibility in FEV_1 of at least 12% of the predicted value after inhalation of 400 μg salbutamol [8,9]. The purpose of the study was explained. Full medical history along with clinical examination were performed for all patients (demographic data for all the patients was noted along with the physiological parameters like blood pressure, respiratory rate, and pulse rate). Patients were assessed for any cardiovascular disease risk factors including the presence or absence of medically diagnosed hypertension and diabetes mellitus. Patients were then subclassified into two: first, according to asthma severity into mild, moderate, and severe (20 patients in each group) and then according to asthma control (controlled, poorly controlled, and uncontrolled) with reference to modified Global Initiative for Asthma (GINA) guidelines [8,9]. The importance of evaluating asthma control rather than asthma severity was emphasized by The GINA guidelines [10]. Steroid-naive group of patients who did not receive steroid medication before were subclassified as a separate subgroup regardless of asthma severity.

Every patient was treated according to his own degree of asthma severity and control as regards frequency of asthma symptoms per month, waking due to asthma per month, and any asthma symptoms plus any risk factor (s) for exacerbation to achieve the best control for the included improperly controlled patients. So, adequate control and regular daily ICS were recommended for all patients with improperly controlled asthma and also for steroid-naive groups of patients and higher stepping up was considered and adjusted according to patient's symptoms with variable recommended daily doses

accordingly (low, medium or high ICS doses) to achieve well-controlled asthma symptoms.

Follow-up and reviewing response were performed after 2–3 months or according to clinical urgency as regards patient's symptoms (clinical), spirometry (functional), and MDCT (radiological) and it was then considered again once good asthma control has been achieved and maintained for 3 months (i.e. by the end of the sixth month after the beginning of proper treatment) for uncontrolled and asthma-naive patient groups.

Exclusion criteria

Smokers, patients with underlying lung disease other than bronchial asthma, mixed obstructive and restrictive pattern in pulmonary function test, and patients having symptoms of respiratory infection within the last 4 weeks (patients with exacerbations or use of systemic steroids within the last month).

Pulmonary functional assessment

Spirometric functional assessment was performed using Jaeger Master Scobe (Enrich Waston) (version 4.5) (Hochberg, Germany) and by using Spida 5 software; predicted values and the percentage of predicted values of all respiratory parameters were measured: VC–VC% (vital capacity), FVC–FVC%, FEV_1–FEV_1%, and FEV_1/FVC ratio FEV_1–FVC% for each patient based on the patient's height, age, and sex [2]. In the present study, all were assessed according to percentage of predicted. An obstructive defect was indicated by a low FEV_1/FVC ratio, which is defined as less than 70% in adults (following the Global Initiative for Chronic Obstructive Lung Disease criteria), with FVC being more than 80% of predicted. For this obstructive defect, the disease reversibility was then determined based on the increase in FEV_1 or FVC after bronchodilator treatment (i.e. increase >12% and >200 ml in adults) [3].

Computed tomography (multidetector computed tomography)

MDCT was performed using a Siemens scanner (Siemens, Erlangen, Germany). Before the scanning procedure, all patients had an instructed training to achieve breath-hold after full end-inspiration. The lungs were then scanned from the apex down to the base at 1-cm intervals, while the patient was breath-holding at full inspiration in the supine position while using a high-frequency reconstruction algorithm procedure. Scans were then viewed, assessed, and examined by two independent chest radiologists blinded to the study aim [11].

Image acquisition

All included patients underwent two volumetric chest CT examinations: one at full inspiration (total lung capacity) and the other at the end of a normal expiration (functional residual capacity). These scans were then reconstructed with a slice thickness of 3–5 mm and then three planes (sagittal, frontal, and axial) were then obtained automatically. MDCT scans were assessed and then analyzed using automated software designed to segment the different airway generations, thus allowing the measurement of wall area (WA), mean values of inner areas (A_i), and outer area (A_o). WA was calculated as the difference between A_o and A_i (A_o–A_i). The percentage (WA%) was calculated as (WA/A_o)×100. Bronchial wall thickness (BWT) was directly measured (mm). BWT was then graded by severity as none (<1 mm), mild (1–2 mm), moderate (2–3 mm), and severe (≥3 mm) [12]. As airway size may be affected by body size, WA and A_i were normalized and then correlated using standardized body surface area (WA/BSA, A_i/BSA). All measured airway dimensions were measured in a blinded manner.

Image processing and reconstruction

Image analysis of all CT examination images was performed using specialized software (Pulmonary Workstation, version 2; VIDA Diagnostics, Erlangen, Germany).

Serum periostin

Serum periostin was measured (×10 dilution) using an enzyme-linked immunosorbent assay (Periostin/OSF-2 Human ELISA Kit; Phoenix Pharmaceuticals, Casa Grande, Western, United State) [5]. Serum periostin was classified into high when its level is more than 90 ng/ml, intermediate when ≥70–≤90 ng/ml, and low if less than 70 ng/ml [7].

Statistical analysis

The data are expressed as mean±SD, median, range, or percentages. Categorical data were analyzed with the χ^2-test. Regression analysis was done to examine the correlations between pulmonary functions and age-adjusted and sex-adjusted or unadjusted, log-transformed serum periostin concentration, duration of asthma, and smoking history. A statistically significant difference was defined as a *P* value of less than 0.05. All statistical analyses were assessed using the statistical software SPSS version 20.0, package for Windows (IBM Corporation, Armonk, New York, USA).

Results

Nonsignificant statistical values were found among asthmatics and control groups as regards age or

Table 1 Demographic, functional, laboratory, and radiological data among the studied patients

Variables	Asthmatic group	Nonasthmatic (control) group	*P* value
N	60	20	
Sex (female/male)	33/27 (55%/45%)	10/10 (50%/50%)	0.423
Age (mean±SD)	38.76±11.23	33.21±17.35	0.542
BMI (mean±SD)	27.23±15.21	27.17±14.34	0.258
PFT parameters (mean±SD)			
VC% predicted	96.2±20.2	99.7±28.7	0.423
FEV_1% predicted	68.72±11.32	98.98±21.44	<0.001
FEV_1/FVC% predicted	63.26±19.52	102.67±17.42	<0.001
Laboratory parameters (mean±SD)			
Blood eosinophils ($\times 10^9$/l)	0.24±1.23	0.18±1.19	0.05
Serum periostin (ng/ml)	88.9±29.1	85.3±32.2	0.235
Total serum IgE (IU/ml)	81±11.13	33.1±9.32	0.01
Radiological parameters (MDCT) (mean±SD)			
WA/BSA (mm^3/m^2)	7.72±3.1	4.13±5.4	0.01
WA (%)	73.21±41.5	64.34±52.1	0.01
BWT (mm)	2.2±1.31	0.7±1.42	0.05

%, percent of the predicted value in relation to the expected value; BSA, body surface area; BWT, bronchial wall thickening; FEV_1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; Ig, immunoglobulin; MDCT, multidetector computed tomography; PFT, pulmonary function test; VC, vital capacity; WA, airway wall area.

BMI. There was a high significant statistical lower values regarding VC, FEV_1% and FEV_1/FVC% predicted among the asthmatic patients than the nonasthmatic healthy (control) group ($P<0.001$, for each). As regards radiological parameters (MDCT), there were statistically significant higher values regarding WA/BSA, WA, and BWT in asthmatics as compared with the healthy control group. Statistically significant higher laboratory parameters were found among asthmatics than in control groups regarding blood eosinophils and total serum IgE. On the other hand, statistically nonsignificant higher serum periostin was found among asthmatic patients than in nonasthmatic control group ($P=0.235$) (Table 1).

Most of the included asthmatic patients 33/60 (55%) were uncontrolled and the remaining 24/27/60 (45%) were well controlled (Table 2).

Although uncontrolled asthma was found among 40% of mild asthma patients and in 55% of those with moderate asthma, it was significantly higher among patients in the severe asthma subgroup, representing about 70% of patients included (Table 3).

As regards steroid treatment among the included asthmatic group, steroid-naive asthma patients represented 18/60 of the included 60 asthmatics and were significantly higher among those with mild asthma 10/20 (50%) than in those with moderate asthma 8/20 (40%) and on the other hand they were 0/20 (0%) in those with severe asthma (Table 4).

Table 2 Classification of the included 60 asthmatic patients according to asthma control

Variable	Controlled asthma	Uncontrolled asthma
n/*N* (%)	27/60 (45)	33/60 (55)

Statistically significant direct relation was found between increased serum periostin level and asthma severity ($P=0.05$) (Table 5).

There was highly statistically significant increase in serum periostin level among uncontrolled asthmatic patients than those with properly controlled asthma ($P\leq0.001$) (Table 6).

There was a statistically significant direct relation with increased WA/BSA, WA, and BWT with asthma severity ($P=0.05$, for each) (Table 7).

There was a highly statistically significant increase in WA/BSA, WA, and BWT among uncontrolled asthmatic patients than those in the adequately controlled asthma group ($P\leq0.001$) (Table 8).

There was statistically significant direct correlation between blood eosinophils and serum periostin level among the studied patients ($P=0.01$), but no statistically significant direct correlation was found between total serum IgE and serum periostin level among the included patients (Table 9).

There was no statistically significant direct correlation between WA/BSA and WA (%) and serum periostin level ($P=0.51$ and 0.35, respectively). On the other

Table 3 Evaluation of asthma control according to asthma severity

Variables	Mild asthma (20 patients) [*n*/*N* (%)]	Moderate asthma (20 patients) [*n*/*N* (%)]	Severe asthma (20 patients) [*n*/*N* (%)]	*P* value
Asthma control				
Controlled asthma [27/60 (45%)]	12/20 (60)	9/20 (45)	6/20 (30)	0.001
Uncontrolled asthma [33/60 (55%)]	8/20 (40)	11/20 (55)	14/20 (70)	0.001

Table 4 Classification of the included 60 asthmatic patients according to treatment with corticosteroids

Variables	Mild asthma (20 patients) [*n*/*N* (%)]	Moderate asthma (20 patients) [*n*/*N* (%)]	Severe asthma (20 patients) [*n*/*N* (%)]	*P* value
Asthma treatment with corticosteroids				
Nonsteroid treated (steroid-naive) patients	10/20 (50)	8/20 (40)	0/20 (0)	0.001
Steroid treated patients	10/20 (50)	12/20 (60)	20/20 (100)	0.001

Table 5 Relation between serum periostin level and asthma severity

Variable	Mild asthma (20 patients)	Moderate asthma (20 patients)	Severe asthma (20 patients)	*P* value
Serum periostin (mean±SD) (ng/ml)	59.98±22.45	63.54±31.23	71.94±26.17	0.05

Table 6 Relation between serum periostin level and asthma control

Variable	Controlled asthma [27/60 (45%)]	Uncontrolled asthma [33/60 (55%)]	*P* value
Serum periostin (mean±SD) (ng/ml)	68.52±32.13	91.94±62.23	<0.001

Table 7 Relation between radiological parameters (multidetector computed tomography) and asthma severity

Variables	Mild asthma (20 patients)	Moderate asthma (20 patients)	Severe asthma (20 patients)	*P* value
Radiological parameters (MDCT) (mean±SD)				
WA/BSA (mm^3/m^2)	4.81±21.1	5.90±15.3	8.02±16.5	0.05
WA (%)	69.34±12.33	70.89±22.19	76.33±18.5	0.05
BWT (mm)	0.79±5.34	1.98±2.28	3.1±3.22	0.05

BSA, body surface area; BWT, bronchial wall thickening; MDCT; multidetector computed tomography; WA, airway wall area.

Table 8 Relation between radiological parameters (multidetector computed tomography) and asthma control

Variables	Controlled asthma [27/60 (45%)]	Uncontrolled asthma [33/60 (55%)]	*P* value
Radiological parameters (MDCT) (mean±SD)			
WA/BSA (mm^3/m^2)	4.98±33.5	9.52±43.1	<0.001
WA (%)	68.01±22.14	81.34±17.23	<0.001
BWT (mm)	1.12±4.24	3.98±6.32	<0.001

BSA, body surface area; BWT, bronchial wall thickening; MDCT, multidetector computed tomography; WA, airway wall area.

Table 9 Relation between laboratory parameters and serum periostin level among the studied groups

Laboratory parameters	Serum periostin (mean±SD) (ng/ml)			*P* value
	Low (<70)	Intermediate (≥70–≤90)	High (>90)	
Blood eosinophils ($\times 10^9$/l)	0.28±2.15	0.41±3.24	0.59±1.27	0.01
Total serum IgE (IU/ml)	73.3±7.52	80.5±9.34	87.1±11.36	0.35

Ig, immunoglobulin.

hand, highly statistically significant direct correlation was found as regards BWT with increased serum periostin level among the included patients ($P<0.001$) (Table 10).

There was highly statistically significant decreased serum periostin level and BWT among the steroid-treated group of patients than in steroid-naive asthma (nonsteroid treated) patients ($P<0.001$ for each). On the other hand, there was no statistically significant decreased WA/BSA and WA in steroid-treated patients than those in the steroid-naive asthma (nonsteroid treated) group ($P=0.54$ and 0.32, respectively). No statistically significant increase in

VC, FEV_1% and FEV_1/FVC% was predicted in steroid-treated patients than those in the steroid-naive (nonsteroid treated) asthma group of patients (P=0.45, 0.24, and 0.31, respectively) (Table 11).

There was highly statistically significant decreased serum periostin level and BWT among steroid-naive asthma (nonsteroid treated) group of patients after adequate regular daily use of ICS for 6 months with adjusted dose according to their grade of asthma control than before its use (P<0.001 for each). On the other hand, there was nonstatistically significant increase in FEV_1% predicted and FEV_1/FVC% predicted with decreased WA and WA/BSA and after use of ICS in the steroid-naive group (N=18) (P=0.32, 0.54, 0.42 and 0.39, respectively) (Table 12).

There was highly statistically significant decreased serum periostin level and BWT among patients with uncontrolled asthma (N=33) after being adequately and properly controlled (for 6 months) than their baseline uncontrolled states (P<0.001 for each). On the other hand, uncontrolled asthma patients' group showed statistically nonsignificant decrease in WA/BSA and WA and increased FEV_1% predicted and FEV_1/FVC% predicted after being well-controlled

Table 10 Relation between radiological (multidetector computed tomography) parameters and serum periostin level among the studied groups

Variables	Serum periostin (mean±SD) (ng/ml)			*P* value
	Low (<70)	Intermediate (≥70–≤90)	High (>90)	
Radiological parameters (MDCT) (mean±SD)				
WA/BSA (mm^3/m^2)	4.53±23.15	5.42±31.21	5.92±22.43	0.51
WA (%)	60.21±12.23	61.37±23.13	68.14±17.43	0.35
BWT (mm)	1.23±2.15	3.99±4.34	5.93±1.27	<0.001

BSA, body surface area; BWT, bronchial wall thickening; MDCT, multidetector computed tomography; WA, airway wall area.

Table 11 Comparison between improperly steroid treated and steroid-naive and treated groups of patients as regards radiological (multidetector computed tomography) and functional parameters and serum periostin level

Variables	Nonsteroid treated patients (steroid-naive asthma) (*N*=18) (mean±SD)	Steroid treated patients (*N*=42) (mean±SD)	*P* value
Serum periostin (ng/ml)	89.56±32.15	59.98±45.22	<0.001
Radiological parameters (MDCT)			
WA/BSA (mm^3/m^2)	8.41±33.24	7.21±43.13	0.54
WA (%)	77.15±17.23	68.01±27.36	0.32
BWT (mm)	3.23±3.13	1.17±1.23	<0.001
PFT parameters			
VC% predicted	102.4±11.3	107.1±18.0	0.45
FEV_1% predicted	67.2±43.1	68.7±38.5	0.24
FEV_1/FVC% predicted	62.1±7.8	65.9±9.3	0.31

%, percent of the predicted value in relation to the expected value; BSA, body surface area; BWT, bronchial wall thickening; FEV_1, forced expiratory volume in the first second; FEV_1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; MDCT, multidetector computed tomography; PFT, pulmonary function test; VC, vital capacity; WA, airway wall area.

Table 12 Comparison between functional, radiological (multidetector computed tomography) parameters, and serum periostin level before and after inhaled corticosteroid among improperly steroid-treated and steroid-naive (nonsteroid treated) patients

Variables	Steroid naive (nonsteroid treated) patients (*N*=18) (mean±SD)		*P* value
	Before ICS	After ICS	
Serum periostin (ng/ml)	89.56±32.15	73.23±12.44	<0.001
Radiological parameters (MDCT)			
WA/BSA (mm^3/m^2)	8.41±33.24	7.99±1.1	0.32
WA (%)	77.15±17.23	75.33±21.15	0.54
BWT (mm)	3.23±3.13	2.46±1.01	<0.001
PFT parameters			
VC % predicted	96.2±20.2	97.01±21.17	0.35
FEV_1% predicted	68.62±11.32	75.23±17.44	0.42
FEV_1/FVC% predicted	63.26±19.52	67.13±23.24	0.39

%, percent of the predicted value in relation to the expected value; BSA, body surface area; BWT, bronchial wall thickening; FEV_1, forced expiratory volume in the first second; FEV_1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; ICS, inhaled corticosteroid; MDCT, multidetector computed tomography; PFT, pulmonary function test; VC, vital capacity; WA, airway wall area.

compared with their uncontrolled baseline state after 6 months follow-up (P=0.53, 0.33, 0.35 and 0.43, respectively) (Table 13).

After age and sex adjustment, a logistic regression model was used to evaluate the significance of individual indices as regards serum periostin, MDCT, and pulmonary function parameters as indicators for airway narrowing diagnosis, its severity, control, and possible response to ICS. It was found that serum periostin had a high significant indicative value as regards asthma control and severity (P<0.001 for each) and significant value regarding probable adequate response to ICS (P=0.001), with no significant role for asthma diagnosis (P=0.231). As regards radiological parameters (MDCT), WA/BSA and WA had no significant role for asthma diagnosis, severity, control, or possible response to ICS. On the other hand, BWT showed a significant value regarding asthma control and severity and probable adequate response to ICS (P=0.01 for each), with no significant role for asthma diagnosis (P=0.245). Regarding pulmonary function test (PFT) parameters, FEV_1% predicted and FEV_1/FVC% predicted had significant indicative value as regards airway narrowing diagnosis and severity(P=0.01 for each), with nonsignificant role for asthma control or probable adequate response to ICS (Table 14).

Optimal cutoff values of individual predictors (serum periostin and BWT) and their sensitivity, specificity, and accuracy for predicting possible asthma control and adequate response to ICS were analyzed and determined. Cutoff values of 95 ng/ml for serum periostin and 4 mm for BWT were found to have sensitivity, specificity, and accuracy for predicting possible asthma control of 92 and 79%, 85 and 76%, and 93 and 80%, respectively. On the other hand, cutoff values of 80 ng/ml for serum periostin and 3 mm for BWT were found to have sensitivity, specificity, and accuracy for predicting possible adequate response to ICS of 90 and 80%, 80 and 75%, and 91 and 85%, respectively (Table 15).

By computer-generated randomization of asthmatic patients with complete data, multivariate analysis of the patient group identified the optimal cutoff value for probability and was calculated based on the most significant cutoff values in each univariate analysis. Multivariate analysis probability was found to be highest when combined serum periostin and BWT were plotted with each other raising sensitivity, specificity, and accuracy for predicting possible asthma control and adequate response to ICS than each was used individually as a univariate index or value. So combined serum periostin and BWT had the best sensitivity, specificity, and diagnostic accuracy with 100 and 97% sensitivity, 95 and 93% specificity, and 99 and 95% accuracy for predicting both possible asthma control and adequate response to ICS, respectively (Table 16).

Discussion

Asthma is an allergic disease mediated by the Th2 inflammatory process. Woodruff *et al.* [13] found that about half of the patients with mild-to-moderate not on inhaled steroids showed an evidence of T-helper cell inflammation in their airways. For the treatment of asthma, Th2 cytokines antagonists such as IL-4, IL-5, and IL-13 are under investigation, which necessitate identification of asthmatic patients most likely to get benefit from these targeted therapies [14]. Inflammatory pathways in asthmatic airways can be assessed directly through induced sputum, measurement of exhaled gases, and bronchoscopy [15]. These are expensive, invasive, time consuming,

Table 13 Comparison between functional, radiological (multidetector computed tomography) parameters, and serum periostin level before and after proper management in uncontrolled asthma group of patients

Variables	Uncontrolled asthma group of patients (N=33) (mean±SD)		P value
	Before control (uncontrolled)	After proper control	
Serum periostin (ng/ml)	91.94±62.23	78.04±22.13	<0.001
Radiological parameters (MDCT)			
WA/BSA (mm^3/m^2)	9.52±43.1	8.34±51.33	0.53
WA (%)	81.34±17.23	78.42±44.45	0.33
BWT (mm)	3.98±6.32	2.12±3.21	<0.001
PFT parameters			
VC% predicted	95.32±33.14	95.98±24.33	0.32
FEV_1% predicted	69.8.12±24.25	75.42±19.41	0.35
FEV_1/FVC% predicted	62.27±20.33	68.44±33.22	0.43

%, percent of the predicted value in relation to the expected value; BSA, body surface area; BWT, bronchial wall thickening; FEV_1, forced expiratory volume in the first second; FEV_1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; ICS, inhaled corticosteroid; MDCT, multidetector computed tomography; PFT, pulmonary function test; VC, vital capacity; WA, airway wall area.

Table 14 Evaluation of the significance of the individual (univariate) indices as regards serum periostin, multidetector computed tomography, and pulmonary function parameters as indicators for diagnosis of asthma, its severity, control, and possible functional and radiological responses to inhaled corticosteroid

Variables	Diagnosis of asthma		*P* value	Asthma severity		*P* value	Asthma control		*P* value	Response to ICS		*P* value
	Odd ratio	95% confidence interval		Odd ratio	95% confidence interval		Odd ratio	95% confidence interval		Odd ratio	95% confidence interval	
Serum periostin (ng/ml)	1.112	1.01–1.14	0.231	1.253	1.43–1.72	**<0.001**	1.313	1.24–1.97	**<0.001**	1.263	1.19–1.53	**0.001**
Radiological parameters (MDCT)												
WA/BSA (mm^3/m^2)	1.124	1.04–1.22	0.230	1.133	1.15–1.21	0.145	1.145	1.31–1.43	0.246	1.123	1.32–1.41	0.342
WA (%)	1.113	1.02–1.12	0.235	1.122	1.34–1.45	0.132	1.104	1.04–1.10	0.132	1.104	1.14–1.25	0.142
BWT (mm)	1.104	1.05–1.13	0.245	1.235	1.35–1.57	**0.01**	1.135	1.41–1.67	**0.01**	1.107	1.36–1.64	**0.01**
PFT parameters												
VC% predicted	1.126	1.22–1.42	0.232	1.116	1.02–1.14	0.241	1.134	1.09–1.18	0.213	1.176	1.17–1.25	0.211
FEV_1% predicted	1.324	1.11–1.62	**0.01**	1.321	1.18–1.78	**0.01**	1.354	1.07–1.16	0.342	1.142	1.25–1.43	0.135
FEV_1/FVC% predicted	1.245	1.31–1.53	**0.01**	1.265	1.07–1.13	**0.01**	1.123	1.32–1.62	0.232	1.133	1.12–1.42	0.143

%, percent of the predicted value in relation to the expected value; BSA, body surface area; BWT, bronchial wall thickening; CI, confidence interval; FEV_1, forced expiratory volume in the first second; FEV_1/FVC, the ratio of forced expiratory volume in 1 s to forced vital capacity; ICS, inhaled corticosteroid; MDCT, multidetector computed tomography; OR, odd ratio; PFT, pulmonary function test; VC, vital capacity; WA, airway wall area. Bold *P* value 0.01 is significant.

and also are not widely available; thus, measurement of noninvasive biomarkers are beneficial to identify Th2-eosinophilic inflammation for targeted therapies. Periostin, a protein from an extracellular matrix and its deposition in the subepithelial layer of bronchial airways, contributes to their thickening, thus reflecting airway inflammation associated with a greater decline in pulmonary function, as a consequence of airway remodeling, so may predict the response to treatment in poorly controlled severe asthmatic patients [16]. It is important to distinguish asthma severity and the degree of control. Severity may be used to describe the underlying nature or intensity of asthma in the absence of treatment. In patients receiving treatment, asthma severity varied from the minimum level of treatment required to achieve good control and the intensity of exacerbations while receiving appropriate controller therapy. So, asthma severity and control are distinct terms and it is important to note that patients with severe asthma can have good control, and on the other hand, patients with mild asthma can have poor control. The level of asthma control is particularly important for patients as its direct impact on quality of life and physicians need to determine the degree of asthma control in order to decide whether treatment adjustments are required [17]. Steroid-naive group of patients who did not receive steroid medication before were subclassified as a separate subgroup. Every patient was treated according to his own degree of asthma severity and control as regards the frequency of asthma symptoms per month, waking due to asthma per month, and any asthma symptoms plus any risk factor (s) for exacerbation to achieve the best control for the included improperly controlled patients. So, regular daily ICS was recommended for all patients with improperly controlled asthma and steroid-naive groups of patients and higher stepping up was considered and adjusted according to patient's symptoms with variable recommended daily doses accordingly (low, medium, or high ICS doses) to achieve well-controlled asthma symptoms. Follow-up and reviewing response was performed after 2–3 months or according to clinical urgency as regards patient's symptoms (clinical), spirometry (functional), and MDCT (radiological) and it was then considered again once good asthma control has been achieved and maintained for 3 months (i.e. by the end of the sixth month after the beginning of proper treatment) for uncontrolled and asthma-naive patient groups. The GINA guidelines emphasize the importance of evaluating asthma control rather than asthma severity [10]. In the present study, there were highly statistically significant lower values regarding FEV_1% and FEV_1/FVC% predicted among asthmatic patients than among

Table 15 Accuracy, sensitivity, and specificity of the possible optimal cutoff values of serum periostin and bronchial wall thickening percentage for predicting asthma control and probable adequate response to inhaled corticosteroid

Variables	Cutoff values	Asthma control (%)				Response to ICS (%)		
		Sensitivity	Specificity	Accuracy	Cutoff values	Sensitivity	Specificity	Accuracy
Serum periostin (ng/ml)	95	92	85	93	80	90	80	91
BWT (mm)	4	79	76	80	3	80	75	85

BWT, bronchial wall thickening; ICS, inhaled corticosteroid.

Table 16 Accuracy, sensitivity and specificity of the possible optimal cutoff values of combined serum periostin and bronchial wall thickening percentage for predicting asthma control and probable adequate response to inhaled corticosteroid

Variable	Asthma control (%)			Response to ICS (%)		
	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity	Accuracy
Combined serum periostin (ng/ml) and BWT (mm)	100	95	99	97	93	95

BWT, bronchial wall thickening; ICS, inhaled corticosteroid.

nonasthmatic healthy (control) group. As regards the radiological parameters (MDCT), there were significant statistical higher values regarding WA/BSA, WA, and BWT in asthmatics as compared with healthy control volunteers. Significant statistical higher laboratory parameters were found among asthmatics than in control groups regarding blood eosinophils (P=0.05) and total serum IgE (P=0.01) On the other hand, nonsignificant statistically higher serum periostin was found among asthmatic patients than in nonasthmatic control group (P=0.235). This was in agreement with Kanemitsu *et al.* [6] and Hitasha *et al.* [18] who found that in the severe asthma group, serum periostin was nonsignificantly higher (92.8±12.1) than in their control group (89.1±11.4) even more than serum eosinophils or total serum IgE. Katarzyna *et al.* [19] and Conway *et al.* [20] also confirmed the present results and found that higher concentrations of periostin was found among patients with asthma than COPD or control. On the other hand; Nakamura *et al.* [21] did not support the present study results as they did not find any significant differences in sputum-induced or bronchoalveolar lavage periostin concentrations among their included subgroups and the values did not differ significantly from those in controls. This may be explained by the small sample of patients with different asthma and COPD phenotypes that were included in their study. This may be explained as well by the fact that they investigated periostin levels in bronchoalveolar lavage fluid in stable asthmatics and healthy patients and suspected that periostin secretion to the airway lumen may be considered negligible than that found in serum. Sidhu *et al.* [22] also supported the present results and found that epithelial secretion of periostin was mainly basal rather than apical. So this may explain Nakamura *et al.* [21] controversy with the present study results. Wagener *et al.* [23] did not confirm the present study as they suggested that eosinophilic asthma was not the only phenotype associated with higher periostin expression. Walker *et al.* [11], Dame *et al.* [12], and Makoto *et al.* [24] agreed with the present study as they found BWT was a common abnormality in MDCT in asthmatics and also concluded that the prevalence of BWT was significantly higher among asthmatics than in healthy patients. In the present study, most of the included asthmatic patients 33/60 (55%) were classified as uncontrolled and the remaining 24/27/60 (45%) were controlled. Although uncontrolled asthma was found among 40% of patients with mild asthma and in 55% with moderate asthma, it was significantly higher among those with severe asthma representing about 70% of patients included in that group. As regards steroid treatment among the included asthmatic group, steroid-naive asthma patients represented 18/60 of the included 60 patients and were significantly higher among those with mild asthma 10/20 (50%) than in those with moderate asthma 8/20 (40%) and on the other hand they were 0/20 (0%) in those with severe asthma. Stephen *et al.* [25] agreed with the present study results as they found that many patients have inadequately controlled asthma despite understanding and adherence to the recommended treatment modalities for bronchial asthma. These patients were found to have severe disease, and thus are at high risk of frequent exacerbations and death. They also found that asthmatics who are not properly controlled with high-dose ICS along with other controller medications, or those who were in need of additional systemic corticosteroids should be in need of a new therapy that improves their clinical outcomes. Dolan *et al.* [26] also confirmed the present study as they found that the percentage of uncontrolled severe asthma seemed high, possibly owing to poor management of the disease. In the present study, there was statistically significant direct relation with increased serum periostin level with asthma severity. Masako *et al.* [27] and Habernau *et al.* [28] agreed with the present study and observed that patients with higher serum

periostin concentrations had lower FEV_1 and FEV_1/FVC in spite of shorter duration of asthma, thus confirming the fact that periostin is a biomarker indicative of rapid decline in pulmonary function. Kanemitsu *et al.* [6] did not support the present study as they found that serum periostin is a clinically useful marker showing that serum periostin concentrations correlated with an annual FEV_1 decline, independent of the severity of asthma. The present study showed highly significant statistical increase in serum periostin level among uncontrolled asthma patients than those with controlled asthma ($P<0.001$). Although Wagener *et al.* [23] did not agree with the present study regarding the significance of serum periostin neither for the diagnosis nor severity of asthma, but supported the present study as regards its higher significant level among uncontrolled asthmatics included in their study. Jia *et al.* [16] also confirmed the present study and concluded that serum periostin had a promising high significant role for detecting uncontrolled asthma than its severity, thus detecting the group of patients who are at high risk of frequent life-threatening frequent exacerbation and in turn in need for more controller medications than ordinary ones. It is suggested that serum periostin levels were similar or nonsignificant among those with mild-to-moderate airway obstruction to those with severe asthma may be explained by the high-dose ICS therapy used by severe asthmatics that reduced the serum periostin with its downregulation, thus reducing its significance as a severity marker. There was statistically significant direct relation with increased WA/BSA, WA, and BWT with asthma severity ($P=0.05$ for each). There was highly significant statistical increase in WA/BSA, WA, and BWT among uncontrolled asthma patients than those with well-controlled asthma. Carr *et al.* [29] supported the present results and found that the prevalence of BWT was higher among severe asthmatics than in those with mild and moderate asthma and adopted Harmanci *et al.* [30] who found a significant positive correlation of BWT with disease severity. Some investigators reported that BWT was correlated significantly with asthma severity, asthma duration, and difficult asthma control, like Walker *et al.* [11] and Paganin *et al.* [31] studies, but other studies have not found such correlation as in the studies by Park *et al.* [32] and Lynch *et al.* [33]. This controversy may be due to different methods with a variable set of the window level used, number, and size of the studied bronchi and patient selection. There was significant statistical direct correlation between blood eosinophils and serum periostin level among the studied patients ($P=0.01$), but no significant correlation was found between total serum IgE and serum periostin in the present study. There was no statistically significant direct correlation between WA/BSA and WA (%) and serum periostin level ($P=0.51$ and 0.35, respectively). On the other hand, highly statistically significant direct correlation was found as regards BWT with increased serum periostin level among the included patients ($P<0.001$). In support of the present findings, Rajanandh *et al.* [34] who found that there was a progressive increase in airway wall thickness related to serum periostin levels and concluded that subepithelial fibrosis or airway remodeling is one factor that causes steroid resistance in asthma indicating that airway remodeling in some populations may be hyporesponsiveness to ICS and usefulness of measuring serum periostin to predict tissue remodeling. This was not in agreement with Katarzyna *et al.* [19] who found nonsignificant changes in serum periostin level between eosinophilic and noneosinophilic subgroups (131.8 and 141.8 ng/ml, respectively) ($P=0.3$). The lack of significant correlations between serum periostin level and asthma phenotypes in their study may be explained by the small number of included participants along with the variable disease features in their study. Masako *et al.* [27] agreed with the present study and found a weak to moderate correlation between serum periostin levels and peripheral blood eosinophilia with no significance between serum periostin and serum IgE. There was no available comparable studies for the correlation between MDCT findings and serum periostin levels like in the present study. There was highly statistically significant decreased serum periostin level and BWT among steroid-treated patients than in steroid-naive asthma (nonsteroid treated) group of patients ($P<0.001$ for each). On the other hand, there was statistically nonsignificant decreased WA/BSA and WA in steroid-treated patients than those with steroid-naive group of patients (nonsteroid treated) ($P=0.54$ and 0.32, respectively). There was statistically nonsignificant increased VC, FEV_1% and FEV_1/FVC% predicted in steroid-treated patients than those with steroid-naive asthma group of patients ($P=0.45$, 0.24, and 0.31, respectively). James *et al.* [35], Woodruff *et al.* [36] and Boushey *et al.* [37] agreed with the present study as they stated that ICS treatment reduces airway periostin expression and in turn its downregulation, thus high levels of serum periostin may represent a noninvasive marker for persistent airway eosinophilia despite the ICS treatment in patients with uncontrolled asthma (in whom inhaled treatment fail to suppress eosinophilic inflammation) or suggesting asthmatic patients not receiving controller ICS. Makoto *et al.* [5] also supported the present study and found that ICS therapy was associated with a reduction in serum periostin level and was associated with decreased wall thickness, increased FEV_1%, and FEV_1/FVC% predicted and decreased sputum

eosinophils. In contrast to the present study, serum periostin levels have been shown to be increased in patients who were receiving a higher dose of ICS in Kanemitsu *et al.* [38] study. The discrepancy in their results may be related to the differences in patient selection and the severity of asthma. There was highly statistically significant decreased serum periostin level and BWT among steroid-naive asthma (nonsteroid treated) patients after regular daily use of ICS for 6 months according to their degree of asthma control than before its use. On the other hand, there was statistically nonsignificant increased FEV_1% predicted and FEV_1/FVC% predicted along with decreased WA/BSA and WA after use of ICS in the steroid-naive group of patients (*N*=18), thus indicating the more significance of serum periostin level and BWT as predictors for treatment response than did FEV_1% predicted or FEV_1/FVC% predicted. This was in accordance with Woodruff *et al.* [36] who found that in ICS-naive patients 12 weeks of treatment with ICS was associated with a significant reduction in serum periostin of about 4.8 ng/ml (about 10% of the baseline level), but unlike the present study that revealed much more decrease in serum periostin concentration of 16.33 ng/ml (about 18% of the baseline value). This discrepancy may be explained by the more prolonged period of follow-up in the present study. This was also relevant to the interpretation by Kanemitsu *et al.* [14] and Conway *et al.* [20]. Taylor [39] and Szefler *et al.* [40] did not find a relation between baseline periostin level and ICS response. Park *et al.* [32] also agreed with the present results and stated that assessment of airway dimensions using noninvasive MDCT properly identifies airway change, thus useful to accurately evaluate efficacy and patient response to guide controller therapy. There was highly statistically significant decreased serum periostin level and BWT among patients with uncontrolled asthma (*N*=33) after being adequately and properly controlled than their baseline uncontrolled states. On the other hand, uncontrolled asthma patients' group showed statistically nonsignificant decrease in WA/BSA and WA and increased FEV_1% predicted and FEV_1/FVC% predicted after being well controlled compared with their uncontrolled baseline state. Jodie *et al.* [41] and Habernau *et al.* [28] agreed with the present findings and stated that in poorly controlled asthmatics treated with ICSs, periostin concentration became lower than their baseline values while uncontrolled with insignificant increase in spirometric parameters including FEV_1% predicted and FEV_1/FVC%. There were no comparable studies regarding MDCT findings for follow-up of uncontrolled asthmatic patients. After adjusting for age and sex, a logistic regression model that was used to evaluate the significance of the individual indices as regards serum periostin, MDCT, and pulmonary function parameters as indicators for diagnosis of asthma, its severity, control, and possible response to ICS. It was found that serum periostin had a highly significant indicative value as regards asthma control and severity and a significant value regarding probable adequate response to ICS, with nonsignificant role for asthma diagnosis. As regards radiological parameters (MDCT), WA/BSA and WA had nonsignificant role for asthma diagnosis, severity, control, or possible response to ICS. On the other hand, BWT showed a significant value regarding asthma control and severity and probable adequate response to ICS, with nonsignificant role for asthma diagnosis. Regarding PFT parameters, FEV_1% predicted and FEV_1/FVC% predicted had significant indicative value as regards asthma diagnosis and severity, with nonsignificant role for asthma control or probable adequate response to ICS. Woodruff *et al.* [13] and Jia *et al.* [16] agreed with the present findings regarding the significant value of serum periostin for detecting asthma severity and control and its nondiagnostic role for asthmatic patients as it may be elevated in other conditions such as idiopathic pulmonary fibrosis, chronic rhinosinusitis, atopic dermatitis, and proliferative diabetic retinopathy. They suspected that high serum periostin in asthmatics on high-dose ICS was not induced by ICS, because airway periostin expression was markedly reduced with ICS treatment. Such elevation of periostin among this population may so reflect IL-13-mediated inflammatory process that is refractory or inadequately responding to ICS medication. They found that severe asthmatics treated with high doses of ICS, serum periostin elevation was associated with persistent airway eosinophilic inflammation, concluding that serum periostin is considered a novel systemic biomarker reflecting airway eosinophilia resistant to ICS. The present results were also consistent with those found by Habernau *et al.* [28], who stated that serum periostin has shown a more significant predictive value for the assessment of asthma control than severity even more than spirometric function test parameters could do. Optimal cutoff values of individual predictors (serum periostin and BWT) and their sensitivity, specificity, and accuracy for predicting possible asthma control and adequate response to ICS were analyzed and determined. Cutoff values of 95 ng/ml for serum periostin and 4 mm for BWT were found to have sensitivity, specificity, and accuracy for predicting possible asthma control of 92 and 79%, 85 and 76%, and 93 and 80%, respectively. On the other hand, cutoff values of 80 ng/ml for serum periostin and 3 mm for BWT were found to have sensitivity, specificity, and accuracy for predicting possible adequate response

to ICS of 90 and 80%, 80 and 75%, and 91 and 85%, respectively. By computer-generated randomization of asthmatic patients with complete data, multivariate analysis of the patients group identified the optimal cutoff value for probability and was calculated based on the most significant cutoff values in each univariate analysis. Multivariate analysis probability was found to be highest when combined serum periostin and BWT were plotted with each other raising sensitivity, specificity, and accuracy for predicting both possible asthma control and adequate response to ICS than each was used individually as a univariate index or value. So combined serum periostin and BWT had the best sensitivity, specificity, and diagnostic accuracy with 100 and 97% sensitivity, 95 and 93% specificity and 99 and 95% accuracy for predicting both possible asthma control and adequate response to ICS, respectively. The present findings were in accordance with James *et al.* [35] and Jodie and colleagues studies who found that the best cutoff value for serum periostin calculated was 90 ng/ml showing a sensitivity of up to 95 with 83% specificity and with a positive predictive value of 95% for predicted asthma control and severity. Lower cutoff value for serum periostin was found by Makoto *et al.* [5] which was 65 ng/ml, which may be explained by the small number of the included patients with different ages and different assay techniques for serum periostin which was used in their study. No comparable studies were found regarding MDCT cutoff values.

Limitations

The limitations of this study included the small sample size and patients were on varied doses of asthma medications such as ICS/long-acting bronchodilators, which may reflect a poor correlation with PFT, MDCT, and serum periostin levels.

Conclusion

Serum periostin marker and BWT had a significant, sensitive, and accurate clinically relevant indicative value (especially when combined) as regards asthma control and severity and probable adequate response to ICS. Serum periostin could not only be a reliable biomarker for eosinophilic inflammation but also may contribute to the development of airway remodeling as assessed by MDCT.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Venzel S. Asthma phynotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012; **18**:716–725.

2 Rajanandh M, Nageswari A, Ilango K. Pulmonary function assessment in mild to moderate persistent asthma patients receiving montelukast, doxofylline and tiotropium with budesonide: a randomized controlled study. *Clin Ther* 2014; **36**:526–533.

3 Güder G, Brenner S, Angermann CE. GOLD or lower limit of normal definition? A comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012; **13**:13–20.

4 Walford M, Doherty T. Diagnosis and management of eosinophilic asthma: a US perspective. *J Asthma Allergy* 2014; **7**:53–65.

5 Makoto H, Junichi O, Kenta A. Association of airway wall thickness with serum periostin in steroid-naive asthma. *Allergy Asthma Proc* 2016; **44**:37–45.

6 Kanemitsu Y, Beasley R, Hurd S, Kudo E. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009; **360**:985–993.

7 Matsumoto H. Serum periostin: a novel biomarker for asthma management. *Allergol Int* 2014; **63**:153–160.

8 Masoli N, Fabian D, Holt S. Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; **59**: 469–478.

9 Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA, pocket guide for health professionals; updated 2015, Dissemination Committee report. *Allergy* 2016; **59**: 469–478.

10 Rabe K, Adachi M, Lai C. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2014; **114**:40–47.

11 Walker C, Gupta S, Müller N, Hartley B, Kudo E. Computed tomography scans in severe asthma: utility and clinical implications. *Curr Opin Pulm Med* 2012; **18**:42–47.

12 Dame R, Magnussen J, Beren N. Greater parallel heterogeneity of airway narrowing and airway closure in asthma measured by high-resolution CT. *Thorax* 2015; **17**:1163–1170.

13 Woodruff P, Modrek B, Choy D. T-helper type 2-driven inflammation defines major subphenotypes of asthma. *Am J Respir Crit Care Med* 2009; **180**:388–395.

14 Kanemitsu Y, Matsumoto H, Izuhara K. Increased periostin associates with greater airflow limitation in patients receiving inhaled corticosteroids. *J Allergy Clin Immunol* 2013; **132**:305–312.

15 Rajanandh M, Nageswari A, Ilango K, Kudo E, Choy D, Erickson R. Effect of two controller medications with inhaled corticosteroid in mild to moderate persistent asthma patients. *J Med Sci* 2014; **14**:181–186.

16 Jia G, Erickson R, Choy G. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol* 2012; **130**:647–654.

17 Vollme W. Assessment of asthma control and severity. *Ann Allergy Asthma Immunol* 2014; **93**:409–413.

18 Hitasha R, Laurie L, Junya O. Serum periostin in asthma: a potential biomarker for stratification in severe treatment-resistant asthma. *Eur Respir J* 2011; **37**:1119–1127.

19 Katarzyna G, Marta M, King T, Patrycja N. Comparative study of periostin expression in different respiratory samples in patients with asthma and chronic obstructive pulmonary disease. *Pol Arch Med Wewn* 2016; **124**:124–136.

20 Conway S, Izuhara S, Kudo E, Müller N. The role of periostin in tissue remodeling across health and disease. *Cell Mol Life Sci* 2014; **71**:1279–1288.

21 Nakamura Y, Nagashima H, Ohta S. Periostin in the bronchial lavage fluid of asthma patients. *Allergol Int* 2015; **64**:209–216.

22 Sidhu S, Yuan R, Innes A. Roles of epithelial cell-derived periostin in TGF-beta activation, collagen production, and collagen gel elasticity in asthma. *Proc Nati Acad Sci USA* 2010; **107**: 169–175.

23 Wagener Q, Nijs S, Lutter R. External validation of blood eosinophils, FE (NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015; **70**:115–120.

24 Makoto H, Shin M, Hiroshi H. Correlation between airflow limitation and airway dimensions assessed by multidetector CT in asthma. *Respir Med* 2013; **104**:794–800.

25 Stephen P, Petersa G, Fergusonb M. Uncontrolled asthma: a review of the prevalence, disease burden and options for treatment. *Respir Med* 2006; **100**:1139–1151.

26 Dolan C, Fraher K, Bleecker E. Design and baseline characteristics of the epidemiology and natural history of asthma: outcomes and treatment regimens (TENOR) study: a large cohort of patients with severe or difficult to treat asthma. *Ann Allergy Asthma Immunol* 2014; **92**:32–39.

27 Masako M, Hiroki K, Koichi F. Phenotype of asthma related with high serum periostin levels. *Allergol Int* 2015; **64**:175–180.

28 Habernau M, Del Pozo A, Rodríguez V. Role of periostin in uncontrolled asthma. *J Investig Allergol Clin Immunol* 2017; **27**:291–301

29 Carr D, Hibon S, Rubens M. Peripheral airways obstruction on high-resolution computed tomography in chronic severe asthma. *Respir Med* 2014; **92**:448–453.

30 Harmanci G, Kebapci S, Metintas M. High-resolution computed tomography findings are correlated with disease severity in asthma. *Respiration* 2012; **6**:427–433.

31 Paganin F, Seneterre E, Chanez P, Kudo E. Computed tomography of the lungs in asthma: influence of disease severity and etiology. *Am J Respir Crit Care Med* 2011; **153**:125–131.

32 Park C, Müller N, Worthy S. Airway obstruction in asthmatic and healthy individuals: inspiratory and expiratory thin-section CT findings. *Radiology* 2013; **204**:369–375.

33 Lynch D, Newell J, Tschomper B, Erickson R. Uncomplicated asthma in adults: comparison of CT appearance of the lungs in asthmatic and healthy subjects. *Radiology* 2014; **188**:829–833.

34 Rajanandh M, Hartley R, Solberg O. Assessment of various second-line medications in addition to inhaled corticosteroid in asthma patients: a randomized controlled trial. *Clin Exp Pharmacol Physiol* 2014; **205**: 7–13.

35 James F, Irene B, Justin T, Kudo S. Serum periostin in obstructive airways disease. *Eur Respir J* 2016; **47**:1383–1391.

36 Woodruff P, Boushey H, Dolganov G. Genome-wide profiling identifies epithelial cell genes associated with asthma and with treatment response to corticosteroids. *N Engl J Med* 2007; **104**:158–163.

37 Boushey H, Sorkness C, King T. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2010; **352**:1519–1528.

38 Kanemitsu D, Matsumoto H, King T, Izuhara K. Increased periostin associates with greater airflow limitation in patients receiving inhaled corticosteroids. *J Allergy Clin Immunol* 2013; **132**:305–312.

39 Taylor D. Using biomarkers in the assessment of airways disease. *J Allergy Clin Immunol* 2011; **128**:927–934.

40 Szefler S, Wenzel S, Müller N, Brown R. Asthma outcomes: biomarkers. *J Allergy Clin Immunol* 2012; **129**:19–23.

41 Jodie L, Simpson S, Ian A. Periostin levels and eosinophilic inflammation in poorly-controlled asthma. *BMC Pulm Med* 2016; **1**:67–72.