Correlation between Serum IL-23 and Pulmonary Functions in a group of Asthmatic Children

Phoebe N. I. Bishara
Pediatric specialist at the Egyptian Ministry of Health and Population, phoebebishara2@gmail.com

Manal M. Wilson
Department of Clinical Pathology, Faculty of Medicine, Cairo University.

Christine W. S. Basanti
Department of Pediatrics, Faculty of Medicine, Cairo University & Pediatric Allergy and Pulmonology Unite, Cairo.

Hanan M. Osman
Department of Pediatrics, Faculty of Medicine, Cairo University & Pediatric Allergy and Pulmonology Unite, Cairo.

Abstract

Background: Bronchial asthma (BA) is a chronic inflammatory airway disease characterized by episodic reversible airway obstruction. BA is classified into T2 high asthmatic endotype with increased Eosinophils (Eos) and Non-T2/T2 low asthmatic endotype with increased Th17 cells and neutrophils. Interleukin-23 (IL-23) has a pivotal role in BA through the maintenance and activation of Th2 and Th17 cells which are contributors to the pathogenesis and severity of BA. Pulmonary function tests (PF) give information about the mechanics of moving air to and from the alveoli through the trachea-bronchial tree in an objective way.

Aim of the work: to evaluate serum IL-23 levels in asthmatic children compared with healthy controls and to correlate them to PF.

Subjects and methods: A cross-sectional study including 90 children aged from 1 to 12 years old was performed, 50% of children were asthmatic (group 1) and 50% were healthy children serving as a control group (group 2). Asthmatic children were recruited from Allergy and Pulmonology clinic, Children's Specialty Hospital, Cairo University. These patients were divided according to age into 3 subgroups (A, B, and C) with 15 patients in each: (A) those aged between 1- 2.5 years old performed infant PF, (B) those aged between 4- 6 years old performed Impulse Oscillometry (IOS) and (C) those aged between 6-12 years old performed Spirometry. Clinical data were recorded, and a complete blood picture (CBP) including Absolute Eosinophilic count (Eos), total serum Immunoglobulin E (IgE), and serum IL-23 were performed.

Results: IL-23 was significantly higher in asthmatic children than in controls. In subgroup (A); minute ventilation inversely correlated to total serum IgE but not to IL-23. In subgroup (B), IL-23 was higher in patients with abnormal PF, however, it didn't correlate to any PF parameters. In subgroup (C), IL-23 inversely correlated to each of the following post-bronchodilator parameters: FEV1, MEF50, and MEF75.

Conclusion: Serum IL-23 is high in asthmatic children and it strongly and inversely correlated to some post-bronchodilator PF parameters in asthmatic children aged 6-12 years.

Keywords: *Bronchial Asthma, Interleukin-23, Absolute Eosinophilic count, Immunoglobulin E, Pulmonary function.*

INTRODUCTION

Bronchial asthma (BA) is a heterogeneous disease, usually characterized by chronic airway inflammation which is defined by the history of respiratory symptoms such as wheezing, shortness of breath, chest tightness, and cough that vary over time and in intensity, together with variable expiratory airflow limitation (1).

BA affects more than one-third of children from the general population (2). Severe asthma affects approximately 10% of all individuals with asthma (3).

In 2010, the prevalence of BA in primary and preparatory school children in Egypt was 15±3% (4).

T2-high endotype of BA is characterized by increased Eosinophils (Eos) in the airways and epithelial expression of T2 cytokines as Interleukins (IL-4) which induces immunoglobulin E (IgE) production (5, 6, 7, 8), IL-5 which activates eosinophils (Eos) and attracts them to the airways (9), and IL-13 affects the airway epithelium and smooth muscles contributing to airway hyper-reactivity (AHR) and mucous secretion (10).

Non-T2/T2-low endotype of BA is propagated by Th17 cells that produce IL-17 which enhances recruitment of neutrophils in the airways and produces profibrotic cytokines, proangiogenic factors, and collagen with subsequent airway fibrosis with more severe asthma course (11, 12, 13).

Interleukin-23 (IL-23) plays a crucial role in airway inflammation through the activation of T helper 2 (Th2) cells (14, 15, 16) and the maintenance and expansion of Th17 cells (17).

Pulmonary function tests (PF) are used for asthmatic patients to assess changes in lung volume and airflow during inspiration and expiration to determine the degree of airway obstruction (18).

PF gives information about the patient's lung physiology objectively by defining the nature (obstructive, restrictive, or mixed), the site (central or peripheral), and the degree of pulmonary dysfunction (19). Similarly, it is used to follow up on pulmonary diseases and to assess the effect of therapeutic interventions (20).

Aim of the work: to evaluate serum IL-23 levels in asthmatic children compared with healthy controls and to correlate them to pulmonary functions.

Subjects and methods:

This is a cross-sectional study including 90 children aged from 1 to 12 years old; 45 children were asthmatic (group 1) and 45 healthy children were serving as a control group (group 2). This study was conducted in the Allergy and Pulmonology clinic, Children's Specialty Hospital, Cairo University.

Our study included asthmatic children of both sexes not in an acute exacerbation. While children with a history of prematurity, those who required prolonged NICU admission or assisted ventilation, children with other causes of recurrent wheezing, children receiving corticosteroids (systemic and inhaled) at the time of sampling or preceding 2- 3 weeks, or on long-term controller medications for asthma, those with chest wall deformities or obese were excluded.

Both groups (1) and (2) were subjected to laboratory investigations: complete blood picture (CBP) including Absolute Eosinophilic count (Eos), total serum IgE, and serum IL-23.

Total serum IgE level was measured using the AccuBindTM IgE Quantitative method. IL-23 serum levels were measured using a double antibody sandwich enzyme-linked immunosorbent assay (ELISA).

BA was assessed in our cases by PF according to Global Initiative for Asthma (GINA). Patients were subdivided into 3 age subgroups (A, B, and C):

(A): Children aged between 1-2.5 years old "not exceeding 80 cm height" (n=15), performed Infant PF,

(B): Children aged between 4-6 years old (n=15), performed Impulse Oscillometry (IOS)

(C): Children aged between 6-12 years old (n=15), performed Spirometry.

Infant PF was performed using the device the V.4.53 Erich Jaeger Master Screen Babybody (GmbH, Würzburg, Germany). It includes the analysis of tidal flow–volume (TV), forced expirations from either normal inspiration (rapid thoracic compression technique) or total lung capacity (TLC) (raised volume rapid thoracic compression technique), or body plethysmography (21).

Impulse Oscillometry (IOS) and Spirometry were performed using A Jaeger Master Screen system (Jaeger Co, Würzburg, Germany) with a separate arm for each.

IOS is a non-invasive passive measurement of the disturbance in flow and pressure of sound waves during normal tidal breathing at multiple frequencies (22). It measures both small and large airway resistance and resonance capacitance of the lung (23). These measurements are affected mainly by the caliber, elasticity, and inertia of the airways, lung tissue, and thorax (24).

Spirometry is a non-invasive method for measuring the flow and volume of air from full lung inflation by using forced maneuvers in cooperative children older than 4 years of age (25, 26). The difference between the pre and post-bronchodilator results $\geqslant$ 12% means reversible airway obstruction, which confirms the diagnosis of BA (27).

The study design complies with the requirements of the Revised Helsinki Declaration of Bioethics (2008). The study was approved by the scientific ethics committee of the Pediatric department, Faculty of Medicine, Cairo University for revision.

Statistical analysis:

Statistical terms such as range, mean ± SD, median, and percent were used for quantitative data. Qualitative data were described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. The significance of the obtained results was judged at the 5% level.

Chi-square test was used for categorical variables, to compare different groups, Exact test was used instead when the expected frequency is less than 5, and Monte Carlo correction was used for correction for Chi-square when more than 20% of the cells have an expected count less than 5. Mann-Whitney test was used for abnormally distributed quantitative variables, to compare between two studied groups. Spearman coefficient: to correlate between two distributed abnormally quantitative variables.

Results:

The present study enrolled 90 children, ages ranging from 1- 12 years old; 45 asthmatic children from the Allergy and Pulmonology outpatient clinic in Children's

Hospital, Cairo University (group 1), as well as 45 healthy children as a control group (group 2).

Atopic manifestations were presented in our patients in the form of allergic rhinitis (n=23), eczema (n=20), atopic dermatitis (n=14), allergic conjunctivitis (n=8), and drug eruption (n=3). Moreover, the severity of BA was presented as intermittent symptoms (n= 15), mild persistent symptoms (n=11), moderate persistent symptoms (n=14), and severe symptoms (n=5).

Group (1) was subdivided into three equal subgroups according to PF is convenient for age:

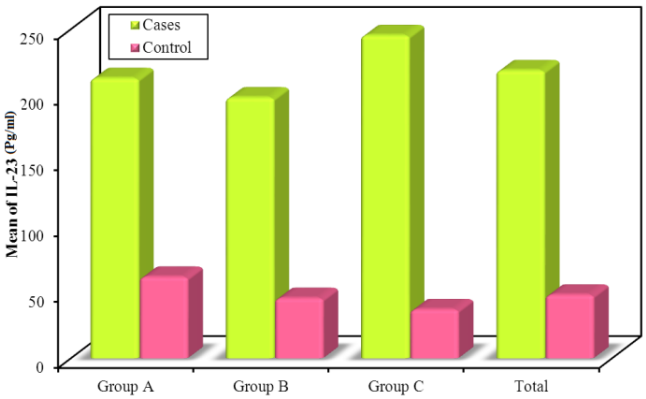
(A): 15 patients (1- 2.5 years old), mean (1.53±0.43) underwent Infant PF.

(B): 15 patients (4- 6 years old), mean (4.67±0.75) underwent IOS.

(C): 15 patients (6-12 years old), mean (8.33±2.19) underwent Spirometry.

Serum IL-23 was significantly higher in the total number of patients (218.71±93.50) than in controls (48.22±41.0) (fig.1). Similarly, Absolute Eosinophilic count was significantly higher in the total number of patients (4.71±2.48) than in controls (1.62±0.91), and also, total serum IgE was significantly higher in the total number of patients (235.71±143.93) than in controls (65.24±86.62), as well as, in each subgroup.

Figure (1): Comparison between cases and controls according to serum IL-23 in total numbers and each subgroup



Serum IL-23 had good specificity and sensitivity for our patient groups as compared to normal control (tab.1).

Table (1): Sensitivity and specificity of serum IL-23 for patients versus controls

	Area under curve	P value	95% Confidence Interval		Cut off value	sensitivity	specificity
			Lower Bound	Upper Bound			
Group A (n=15)	.9600	**< 0.001**	0.897	1.000	178	86.7 %	100 %
Group B (n=15)	0.852	**.0010**	.6970	1.000	175	73.3 %	100 %
Group C (n=15)	0.958	**< 0.001**	.8950	1.000	75.15	86.7 %	93.8%
Total (n=45)	0.930	**< 0.001**	.8760	.9850	178	80 %	100%

In subgroup (A): no significant difference was found between mean serum IL-23 in infants with normal and those with abnormal PF (p= 0.624) (tab.2). However, total serum IgE inversely correlated to minute ventilation (p= 0.030) (tab.3).

Table (2): Comparison between normal and abnormal PF considering serum IL-23 in subgroups (A), (B), and (C)

IL-23	Pulmonary function		U	p
	Normal	Abnormal		
Group A (n= 15)	**(n=10)** 205.04 ± 76.46	**(n=5)** 228.12 ± 20.66	21.0	0.624
Group B (n= 15)	**(n=9)** 157.40 ± 108.0	**(n=6)** 259.02 ± 50.41	8.00	**0.025***
Group C (n= 15)	**(n=7)** 258.90 ± 115.59	**(n=8)** 233.51 ± 110.34	25.0	0.728

U, p: U and p values for Mann Whitney test for comparing between the two groups

*: Statistically significant at p ⩽ 0.05

Table (3): Correlations between Infant PF parameters and total serum IgE, and serum IL-23 in the subgroup (A)

Pulmonary functions	IgE**		IL-23	
	rs	p	r_s	P
Tv	-0.102	0.718	-0.073	0.795
Vmax	-0.450	0.092	0.043	0.879
Mean sRaw	0.120	0.671	-0.396	0.143
Minute vent.	-0.559	**0.030#**	0.054	0.850
t_{PTEF}/t_E	-0.004	0.990	0.020	0.944
tPTEF/tE	-0.004	0.990	0.020	0.944

IgE**: Immunoglobulin E rs: Spearman coefficient #: Statistically significant at p ⩽ 0.05

In subgroup (B): A statistically significant difference was found between mean serum IL-23 in children with normal and in those with abnormal PF done by IOS (p= 0.025) (tab.2). However, there was no significant correlation between mean serum IL-23 and any individual IOS parameters (tab.4).

In subgroup (C): no significant difference was found between mean serum IL-23 in children with normal and in those with abnormal PF (p= 0.728) done by spirometry (tab.2). However, serum IL-23 inversely correlated to each of the following post-bronchodilator parameters done by spirometry: FEV1 (p= 0.038), MEF50 (p=0.018) and MEF75 (p=0.025) (tab.5).

Table (4): Correlation between serum IL-23 and IOS parameters in the subgroup (B)

Pulmonary functions	IL-23	
	r_s	P
R5	0.427	0.113
Post r5	-0.077	0.812
R20	0.432	0.108
Post r20	0.014	0.965
X5	0.500	0.667
Post x5	-0.109	0.737
Ax	0.264	0.342
Post Ax	-0.503	0.095

rs: Spearman coefficient

Table (5): Correlation between serum IL23 and different Spirometry parameters in the subgroup (C)

Pulmonary functions	IL-23	
	r_s	P
FEV1	-0.191	0.494
Post FEV1	-0.539	**0.038***
MEF25	-0.445	0.096
Post MEF25	-0.511	0.052
MEF50	-0.280	0.313
Post MEF50	-0.599	**0.018***
MEF75	-0.338	0.218
Post MEF75	-0.575	**0.025***
FEV1/FVC	-0.075	0.791
Post FEV1/FVC	-0.046	0.869

rs: Spearman coefficient

*: Statistically significant at p ⩽ 0.05

Discussion:

Interleukin-23 (IL-23) is a member of the IL-12 family, produced mainly by activated macrophages and dendritic cells in the peripheral blood (28, 29). IL-23 has a specific role in BA as it helps in Th2 and Th17 differentiation with the production of IL-17 and different cytokines recruiting both Eos and neutrophils to the airways (30)

In the present study, serum IL-23 levels were significantly higher in the studied patients than in the controls. These results were in concordance with other researchers, who found that IL-23 levels were higher in asthmatics than in controls (30). This is explained as IL-23 is an adjunctive Th17-associated cytokine involved in the worsening of inflammatory phenomena and it might modulate allergic inflammation influencing Th2 differentiation (31, 32, 33, 34, 35).

In addition, Absolute Eosinophilic count and total serum IgE were significantly higher in our patients than in the controls. These results were in concordance with others, who reported asthmatic patients had higher Absolute eosinophilic count and total serum IgE levels compared to controls(36, 37), which is explained as high Absolute eosinophilic count in peripheral blood and airway secretions is one of the hallmarks of BA (38), and they are contributors in the development of BA especially the atopic phenotype (39).

In our study, there was a significant difference between the 3 subgroups regarding the correlation between some PF parameters and blood biomarkers for BA.

In subgroup (A), A statistically significant inverse correlation between total serum IgE and minute ventilation was noted. This could be explained by the correlation between high serum total IgE levels and bronchial hyper-responsiveness and asthma (40), and the minute ventilation is dependent on the tidal volume, which decreased in asthmatic patients. Hence, the inverse correlation.

However, no significant correlation was found between Absolute Eosinophilic count, total serum IgE, or serum IL-23 with the mean of the specific resistance (sRaw). sRaw is the product of airway resistance (Raw) and Functional residual capacity (FRC) and both increase in the presence of airway obstruction and hyperinflation. This could be explained by the small sample size within the group.

In subgroup (B), we documented a statistically significant difference between serum IL-23 in children with normal and those with abnormal PF done by IOS, as IL-23 has a pivotal role in the inflammation of the airways through activation and maintenance of Th2 and Th17 cells and the recruitment of Eosinophils and neutrophils into the airways (41). However, serum IL-23 did not correlate with any individual IOS parameters.

In subgroup (C), our study is consistent with the finding of another study that documented a statistically significant inverse correlation between serum IL-23 and post-bronchodilator FEV1 due to the possible negative influence of IL-23 on bronchial airflow (42).

In addition, our work recorded no correlation between serum IL-23 and FEV1/FVC ratio (pre or post-bronchodilators). On contrary, others found a strong inverse relationship between serum IL-23 and FEV1/FVC ratio (42), which is supported by another study, that reported low FEV1/FVC ratios in children with persistent wheezing (43). This discrepancy could be explained by the fact that we selected patients, not in any exacerbation and FEV1 might be within the normal range in between the attacks.

In our study, most of the post-bronchodilator parameters showed improvement in comparison with the pre-bronchodilator parameters. Moreover, we

found a statistically significant inverse correlation between serum IL-23 and each of the following post-bronchodilator parameters done by spirometry: MEF50 and MEF75. This was due to patients with high serum IL-23 levels having lower post-bronchodilator parameters than those who had lower serum IL-23. This means that patients with higher serum IL-23 showed less response to bronchodilators which may be a predictor of asthma severity.

These results were in agreement to some extent with other investigators who reported an inverse correlation between serum IL-23 level and PF in asthmatic children (35) and a direct association between serum IL-23 and the severity of BA (44).

This was supported by other studies which hypothesized; IL-23 enhances Th2 type immune reaction with Eos production, airway inflammation, and hyper-responsiveness and promotes differentiation and survival of Th17 cells with production of IL-17 (45) that evokes migration of neutrophils to airways with progression to severe BA and decrease in PF (46).

Limitations of the study

The results of our study need further verification on large-scale studies as the sample size within each group was small.

Conclusion

Serum IL-23 levels were increased in asthmatic children and inversely correlated to some post-bronchodilator PF parameters. Therefore, specific roles for IL-23 in BA are currently emerging; IL-23 can be a complementary marker along with clinical criteria for diagnosis of asthma in children more than 6 years old and a good marker for follow-up of treatment, and prognosis of asthmatic patients. It has a promising role in IL-23 targeted therapy.

Reference

Global Initiative for Asthma (GINA) (2017): A Pocket guide for asthma management and prevention (for adults and children older than 5 years). Available at www.ginasthma.org, accessed on April 1, 2017.

Janahi IA, Bener A and Bush A (2006): Prevalence of asthma among schoolchildren: International Study of Asthma and Allergies in Childhood, Qatar. Pediatr Pulmonol; 41: 80- 86.

Chastek B, Korrer S, Nagar SP, et al. (2016): Economic burden of illness among patients with severe asthma in a managed care setting. J Manag Care Spec Pharm; 22: 848- 861.

El-Falaki MM, Korani M, Hassan M, et al. (2018): Prevalence of Bronchial Asthma and Other Allergic disorders in a Sample of Egyptian Children from Cairo and Giza Governorates. Master Thesis, 2018.

Ortega HG, Yancey SW, Mayer B, et al. (2016): Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med; 4: 549- 556.

Becerra-Díaz M, Wills-Karp M and Heller NM (2017): New perspectives on the regulation of type II inflammation in Asthma. F1000 Research; 6: 1-19.

Dunican EM and Fahy JV (2015): The Role of Type 2 Inflammation in the Pathogenesis of Asthma Exacerbations. Annals of the American Thoracic Society; 12: 144- 149.

Rijt L, Richthofen H and Ree R (2016): Type 2 innate lymphoid cells: at the crossroads in allergic asthma. Semin Immunopathol; 38: 483- 496.

Borish L (2016): The immunology of asthma: asthma phenotypes and their implications for personalized treatment. Ann Allergy Asthma Immunol; 117: 108-114.

Gour N and Wills-Karp M (2015): IL-4 and IL-13 signaling in allergic airway disease. Cytokine; 75: 68-78.

Parulekara AD, Diamant Z and Hanania NA (2017): Role of biologics targeting type 2 airway inflammation in asthma: what have we learned so far? Curr Opin Pulm Med; 23: 3- 11.

Al-Muhsen S, Letuve S, Vazquez-Tello A, et al. (2013): Th17 cytokines induce profibrotic cytokines release from human eosinophils. Respir Res; 14: 34-45.

Hoppenot D, Malakauskas K, Lavinskiene S, et al. (2015): p-STAT6, PU.1, and NF-κB are involved in allergen-induced late-phase airway inflammation in asthma patients BMC Pulmonary Medicine; 15: 122-133.

Heck S, Nguyen J, Le D, et al. (2015): Pharmacological Therapy of Bronchial Asthma: The Role of Biologicals. Int Arch Allergy Immunol; 168: 241- 252.

Nakajima H and Hirose K (2010): Role of IL-23 and Th17 Cells in Airway Inflammation in Asthma. Immun Network; 10: 1- 4.

Haworth O, Cernadas M, Yang R, et al. (2008): Resolvin E1 regulates interleukin 23, interferon-γ, and lipoxin A 4 to promote the resolution of allergic airway inflammation. Nat.Immunol; 9: 873- 879.

He D, Wu L, Kim HK, et al. (2006): CD8+ IL-17 producing T cells are important in effector functions for the elicitation of contact hypersensitivity responses. J Immunol; 177: 6852- 6858.

Lee MS, Kao JK, Lee CH, et al. (2013): Correlations between Pulmonary Function and Childhood Asthma Control Test Results in 5- 11 Year Old Children with Asthma. Pediatr Neonat; 55: 218- 224.

Anandi S, Tullu MS and Lahiri K (2016): Evaluation of symptoms & spirometry in children treated for asthma. Indian J Med Res; 144: 124- 127.

Castile RG (2006): Pulmonary Function Testing in Children. In: Kendig's Disorders of the respiratory tract in children, 7th edition. Chernick V, Boat TF, Wilmott RW, et al. (eds). Elsevier Inc; P168- 169.

Moeller A, Carlsen KH, Sly PD, et al. (2015): Monitoring asthma in childhood: lung function, bronchial responsiveness, and inflammation. Eur Respir Rev; 24: 204-215.

Desiraju K and Agrawal A (2016): Impulse oscillometry: The state-of-art for lung function testing. Lung India; 33: 410-416.

Saadeh C, Cross B, Saadeh C, et al. (2014): Retrospective Observations on the Ability to Diagnose and Manage Patients with Asthma through the Use of Impulse Oscillometry: Comparison with Spirometry and Overview of the Literature. Pulmonary Med; P 1- 9.

Goldman MD, Saadeh C and Ross D (2005): Clinical applications of forced oscillation to assess peripheral airway function. Respir Physiol Neurobiol; 148: 179- 194.

Ferguson GT, Enright PL, Buist AS, et al. (2000): Office spirometry for lung health assessment in adults: a consensus statement from the National Lung Health Education Program. Chest; 117: 1146-1161.

Bacharier LB and Guilbert TW (2012): Diagnosis and management of early asthma in preschool-aged children. J Allergy Clin Immunol; 130: 287- 296.

Stanojevic S, Wade A and Stocks J (2010): Reference values for lung function: past, present and future. Eur Respir J; 36: 12-19.

Langrish CL, Chen Y, Blumenschein WM, et al. (2005): IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J exp med; 201: 233- 240.

Uhlig HH, McKenzie BS, Hue S, et al. (2006): Differential activity of IL-12 and IL-23 in mucosal and systemic innate immune pathology. Immunity; 25: 309- 318.

Alyasin S, Amin R, Fazel A, et al. (2017): IL-23 Gene and Protein Expression in Childhood Asthma. Iran J Immunol; 14: 73-80.

Ciprandi G, Cuppari C, Salpietro A, et al. (2012a): Serum IL-23 in asthmatic children. J Biol Regul Homeost Agents; 26: 53- 61.

Ciprandi G, Cuppari C and Salpietro C (2012b): Serum IL-23: a surrogate biomarker for asthma. Clin Exp Allergy; 42: 1416- 1417.

Abdulkareem ZT and AL-Saadi BQH (2021): Gene Expression and Serum IL-23 in Asthmatic Iraqi Children. Indian J of Forensic Med & Toxicol; 15: 1686- 1693.

Jabbar BA, AL-Hasnawi ATN, Hussein AM, et al. (2022): Elevated serum levels of interleukin -22 and interleukin-23 in pediatric asthma. Int J of Health Sciences; 6: 3931-3944.

Wu AY and Peebles RS (2023): The emerging role of IL-23 in asthma and its clinical implications. Exp Review of Clin Immunol; 19:1-5.

Mosayebian A, Hakemi MG, Meshkat R, et al. (2015): Association between Interleukin-23 Receptor R381Q Gene Polymorphism and Asthma. Iran J Allergy Asthma Immunol; 14: 386- 391.

Al-Quraishi GMS (2013): Serum Levels of Total IgE, IL-12, IL-13 and IL-18 in Children Patients with Asthma. Iraqi J Pharm Sci; 22: 110- 114.

Haldar P and Pavord ID (2007): Noneosinophilic asthma: a distinct clinical and pathologic phenotype. J Allergy Clin Immunol; 119: 1043- 1052.

Mackay IR and Rosen FS (2001): Asthma. N Engl J Med; 344: 350- 362.

Depner M, Fuchs O, Genuneit J, et al. (2014): Clinical and epidemiologic phenotypes of childhood asthma. Am J Respir Crit Care Med; 189: 129- 138.

Li Y and Hua S (2014): Mechanisms of pathogenesis in allergic asthma: Role of interleukin-23. Respir; 19: 663- 669.

Ciprandi G, Cuppari C and Salpietro C (2012c): Serum IL-23: a surrogate biomarker for asthma. Clin Exp Allergy; 42: 1416- 1417.

Chatkin MN, Menezes AMB, Macedo SEC, et al. (2008): Asthma and lung function in a birth cohort at 6-7 years of age in southern Brazil. J Bras Pneumol; 34: 764-771.

Guan Q, Ma Y, Aboud L, et al. (2012): Targeting IL-23 by employing a p40 peptide-based vaccine ameliorates murine allergic skin and airway inflammation. Clin Exp Allergy; 42: 1397- 1405.

Peng J, Yang XO, Chang SH, et al. (2010): IL-23 signaling enhances Th2 polarization and regulates allergic airway inflammation. Cell Res; 20: 62- 71.

Molet S, Hamid Q, Davoine F, et al. (2001): IL-17 is increased in asthmatic airways and induces human bronchial fibroblasts to produce cytokines. J Allergy Clin Immunol; 108: 430- 438.