

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Immunological Study in Patients with Allergic Asthma.

Talib Abdullah Hussein¹, Suaad Almas. Brakhas², and Sura Muslim Dawood^{3*}.

¹Department of Biology, College of Science for Women ,University of Baghdad/Iraq.

²Department of Immunology –Allergy Specialized Center, Baghdad / Iraq .

³Department of Biology ,College of Science for Women ,University of Baghdad /Iraq

ABSTRACT

This Study was design to shed the light on the causative inhalant allergens of allergic asthma in Iraqi environment and diagnosis it by detected of Total and specific IgE for some Indoor and outdoor inhalant allergens and IL-13, IL-18 in allergic asthma. A highly significant differences in total and specific IgE between asthma patients and control. The measurement of serum specific IgE for some inhalant allergens (HDM, Pits, Cockroach, Mites, Grasses pollen, Tree pollen and Weed pollen) allergens for all subject by used Western Immunoblotting test in Euro line Inhalation Profile Kits . In asthmatic patients , the **i6** allergen had highest percent fallow by pets allergens (**E**) , Grasses pollen (**G**).A highly significant differences in IL-13 and IL-18 levels between allergic asthma group and control .

Keywords: Serum total IgE,Spesific IgE , Allergic asthma.IL-13, IL-18.

**Corresponding author*

INTRODUCTION

In type-1 of allergy , the response of immune system against allergen occurs immediately by IgE antibody, it binds with a specific receptors on mast cells and basophiles that lead to activate it and starting several sequential cellular and molecular reaction that cause clinical signs and symptom of allergic diseases [1]. The continuous exposure to common environmental allergens may lead to acute and chronic allergy [2]. Asthma is a various disorders in respiratory system which is characterized by airflow obstruction causing by inflammation bronchial hypersensitivity, that leads to breathlessness, coughing, and wheezing .There are more than 300 million of people suffering from asthma and they represent (10-15)% of world population[3, 4]. There are different risk factors that are associated with allergic asthma which include genetic and environmental factors such as indoor inhaled allergen and outdoor allergens [5 , 6]. IgE is a fifth class of immunoglobulin plays a role in defense mechanism against protozoa ,parasites , helminthes and it is a main mediator in allergy [7]. which includes allergic asthma , allergic rhinitis ,anaphylaxis and atopic dermatitis[8]. It use in diagnosis of allergy followed by the detection of specific allergens [9]. Allergens are plant or animal proteins which are able to generate IgE responses and allergic disease in the exposed individual. They are a main risk factor for Allergic Rhinitis (AR), Allergic Asthma (AA) and Allergic Conjectivitis AC. [10]. Inhalator allergens are aeroallergens, they are aerosols its size from submicron allergens to moderately larger allergens (pollen grains, spores of fungi, animal allergens, and others [11]. In House Dust Mites (D) there are two common genus (*Dermatophagoides pteronyssinus*) and (*Dermatophagoides farinae*) [12]. Tree Pollens (T) (Alder, birch, oka, olive), Grasses (G) (Rye, Timothy) and Weeds(W) (Ragweed, Mugwort) [10]. Moulds(M) (*Penicillium*, *Cladosporium*, *Aspergillus*, *Candida*, *Alternaria*)[13] Dander (Cat, Doge, Horse, Camel) [10]. Interleukin -13 is a cytokine that produced by T-helper type 2 (Th2) [14]. It is a essential cytokine in mechanism of allergic diseases through their effect on IgE synthesis, increase secretion of mucus which in turn is responsible for shortness of breath, obstruction in asthmatic patients and fibrosis [15] , So it is a main target to treat allergy [16]. Interleukin-18 is Th2 cytokine; it is a pleiotrophic and proinflammatory cytokine. It is one of the IL-1 family, it contributes in differentiation of Th1 and Th2. [17]. Many cells produce these cytokine for example basophils, mast cell, Nateral Killer cell (NK) and T cells. [18]. Epithelial cells are a main producer for pro-allergic cytokine such as IL-18(19).

MATERIALS AND METHODS

The Total allergic patients were [99 (43 male),(56 female)] and Apparently Healthy Control [40 (15 male),(25 female)]. Their age group (5-60) years collected from Specialized Center Of Allergy in Baghdad /AL-Resafa and during the period from October 2016 to February 2017..Identify the Total IgE,IL-13 and IL-18 serum level by used ELISA technique and T-IgE kit (Euroimmune , Germany) , IL-13 kit (CUSABIO,China) and IL-18 Kit (CUSABIO, China). Detected the Spesific IgE serum by used Western Immunoblotting test in Euro line Inhalation Profile Kits (Euroimmune, Germany), it is multi-parameter assay containing 20 of the most common inhalator allergens as shown in table (1) below .

Table 1: The abbreviation of inhalant allergens .

Series	Allergen code	Name of Allergen	Serie s	Allergen code	Name of Allergen
1-	G6	Allergen of Timothy Grass	11-	I6	Allergen of Cockroach ,Germany
2-	G12	Allergen of Cultivated Rye	12-	E1	Allergen of the Cats
3-	T2	Alder Allergen of	13-	E2	Allergen of the Dogs
4-	T3	Birch Allergen of	14-	E3	Allergen of the Horse
5-	T7	Allergen of oak	15-	E17	Allergen of the Camels
6-	T9	Allergen of Olive	16-	M1	Allergen of the <i>Penicillium notatum</i> spores
7-	W1	Common ragweed Allergen of	17-	M2	Allergen of <i>Cladosporium herbarum</i> spores
8-	W6	Allergen of Mugwort	18-	M3	Allergen of the <i>Aspergillus fumigatus</i> spores
9-	D1	Allergen of <i>Dermatophagoides pteronyssinus</i>	19-	M5	Allergen of the <i>Candida albicans</i> . spores
10-	D2	Allergen of <i>Dermatophagoides farina</i>	20	M6	Allergen of the <i>Alternaria alternate</i> spores

Statistical Analysis: The usual statistical methods were used in order to assess and analyze the results; they include:

I-Descriptive statistics : (observed frequencies, percentages, mean standard deviation, standard error & cumulative percentage (%)) and Graphical presentation through using Bar.
II-Inferential Statistics: They were used in order to accept or reject the statistical hypotheses; they include (Chi-Square test (χ^2), Binomial test (Z-test), Analysis of variations (ANOVA) with multi comparison, less significant difference (LSD) test) [20].

RESULTS

Immunological Study: The Results of the Serum level Total IgE (T-IgE).

The table (2) .The (mean \pm SE) of serum T-IgE in asthmatic patients (**313.713 \pm 13.633 IU/ml**) as compared with control (**30.625 \pm 3.843 IU/ml**). A highly significant differences between asthma patients and control (**P=0.00**), (**P<0.01**) . The specific inhalant allergens as shown in table (3), there were highly significant differences between asthmatic patients how had specific IgE to inhalant allergens(positive), their number percent was(**78** , **78.79%**) and negative patients (**21** , **21.21%**). There were highly significant differences between positive and negative group (**P=0.00**),(**P<0.01**). In asthmatic patients , the **i6** allergen had highest percent Cockroach (**i6 = 84.85%**) , fallow by pets allergens Pets (**E= 42.42%**) , Grasses pollen(**G= 30.30%**) as shown in figure (1). As shown in table below (4). A highly significant differences in IL-13 level between asthmatic patients and control (**P =0.00**), (**P<0.01**), the mean \pm SE of IL-13 in asthmatic patients were (**1145.728 \pm 81.161 ng/ml**) as compared with control (**546.016 \pm 8.285 ng/ml**) . A highly significant differences in IL-18 level (**P=0.005**),(**P<0.01**) ,the IL-18 level (mean \pm SE) of asthmatic patients (**70.711 \pm 6.767 ng/ml**) as compared with control patients were (**42.312 \pm 2.535 ng/ml**).

Table 2: The Distribution of T-IgE with Studied group.

Immunological assay		N	Mean	Std. Deviation	Std. Error	P – value
						LSD test
Total IgE	Asthma	99	313.713	135.646	13.633	P=0.00 HS
	A.H. control	40	30.625	24.304	3.843	
	Total	139				

Table 3: The Results of Serum Level Specific IgE to Inhalant allergens.

Asthma		N	%	Binomial (Z) test
Inhalation (Total)	Positive	78	78.79	P=0.00 Highly sign. (P<0.01)
	Negative	21	21.21	
	Total	99	100	

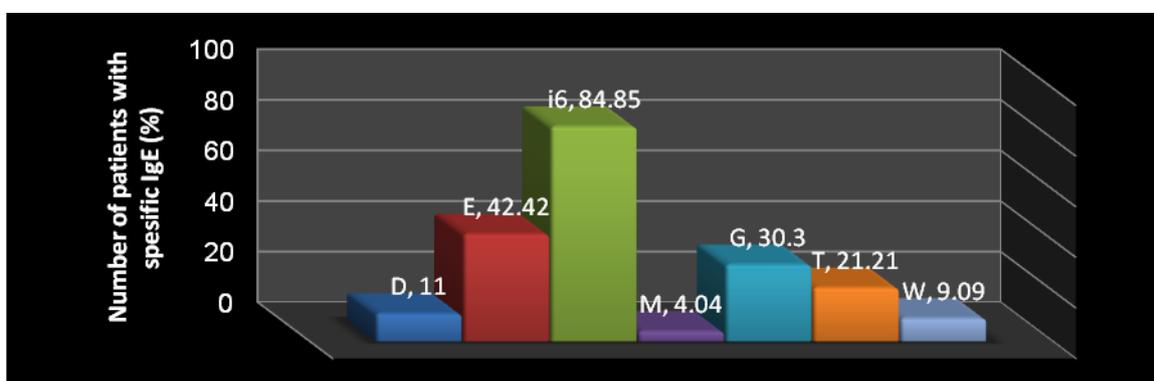


Figure (1): The Distribution of inhalant allergens.

Table (4): The Results of The Serum Level IL-13.

Immunological assay	N	Mean	Std. Deviation	Std. Erroe	P- Value
					LSD Test
IL-13 (ng/ml)	Asthma	99	1145.728	513.301	81.161
	A.H. control	40	546.016	52.399	8.285
	Total	139			
					P=0.00 HS
IL-18 (ng/ml)	Asthma	69	70.7115	42.796	6.767
	A.H. control	40	42.312	16.031	2.535
	Total	139			
					P=0.002 HS

DISCUSSION

This results of total IgE agree with several studies in Iraq , the results of Rasheed and Brakhas [21 , 22] they showed that the level of T-IgE significantly increase in asthmatic and rhinitic patients when compared with control. In studies of Wahhab [23] he showed that there were a significant increase in level of T-IgE in asthma patients. In study of Baldo and Desa [24,25] they found that the high level if T IgE in allergic patients as compared with control. Also Zietkowski [26] study showed that the IgE increase significantly in asthmatic patients as compared with control. The allergic asthma mechanism lead to increase in total IgE levels in allergic patients [27 , 28].The TIgE level increase with parasitic infection and allergic disease (type -1 hypersensitivity),it bind with specific receptors (Fc Epsilon RI) on mast cell and basophil cells surface ,that lead to cross-linked between IgE Ab, rapture of cell surface and release mediators which responsible for allergic symptoms.

The exposure to inhalant allergens may occur in every place, human through practices his normal life daily; he cannot avoid exposure to pollution, chemical materials, car fumes, dust and inhalant allergens which causes allergy.The results of specific inhalant allergens was in agreement with some studies in Iraq, Rasheed[29] found from 128 patients there were 80(62%) had positive specific IgE and 48(38%) had negative. Rasheed [21] found that the S IgE test was positive in 62.5% of patients and total positive aeroallergens was (91%). Wahhab [23] Recorded results which were the percentage of positive allergen patients (94.6%) while negative patients percentage (5.4%)..Allergens play great role in pathogenesis of allergic diseases [31]. Many studies in Iraq done by Alwan [30] who founded that the HDM and pollens had a highest percentage among inhalant allergens . In theWahhab [23] study who reported that the highest percentage for HDM(D)=86.5% , followed by Mites (M)=73%.The results of Rasheed [29] study appear that the highest percentage for Grass pollen(G=41.7%) , followed by tree pollen (T=36% , E=25% , D=22.5%) in serum of patients with respiratory allergy. The study of Rasheed [21] study who regarded that the highest percentage for grasses (G=41.70%) , fallow by (T= 36% , E=25% , D=22.5%) in allergic patients . The results of Lokaj-Berisha [32] appeared that the house dust mite was a highest percentage among inhalant allergens followed by pollens. In Iran Assarehzadegan [33] study showed that the pollens as the major allergens fallow by mite, mold .The study of Farrokhi [40] he recorded that the HDM had the maximum rate of sensitization (41.2 % , 88.5%).This variation in results may be due to variation in age, associated diseases & geography of studies and environmental factors .The main allergens was i6 for (Cockroach) in asthmatic patients. In August/2016 the Cockroch that are sweeping Basra, Baghdad, Diala in large numbers , may be imported from outside the country that due to climate changes, the heat wave. This problem is not limited to Iraq but also suffer from some neighboring countries also, Especially Kuwait and Saudi Arabia. The spread of "cockroaches" in the capital Baghdad came because the high level of sewage due to rain caused the spread of cockroaches in the capital.

The results of IL-13 was in agreement with Al-Quraishi study [34] in Iraq who found that the IL-13 level in serum was significant increase in children with asthma as compared to control. The results of Wioletta [35] study showed that the IL-13 level were significantly increase in asthma and rhinitis patients. The study of Panaitescu [36] who regarded that the IL-4 and IL-13 had a important role in development of allergic disease mechanism in HDM allergic patients, IL-4 is more essential than IL-13 for specific IgE production and IL-13 is most important cytokine for total IgE production. The serum eotaxin, IL-13 and Total IgE levels were significantly increase in the asthma group as compared to control, Serum IL-13 and eotaxin correlated with severity of bronchial asthma [37]. The serum IL-13 level increased in asthma and correlated with asthma severity and Chronic Obsrtuctive Pulmonary Disease [38] So, IL-13 play a role in asthma pathogeneses and it a target to treated asthma [39].In study of Panaitescu [36] who reported that IL-4 and IL-13 had a role in development of

HDM allergic asthma and rhinitis. Adjers [41] published that the IL-13 allele was high prevalence in allergic rhinitis with asthma. The IL-13 play as a good indicator of allergic disease and asthma [42]. IL-13 produced by Th2 cell, Interleukin 13 is an essential cytokine in mechanism of allergic diseases through their effect on IgE synthesis, increase secretion of mucus which in turn is responsible for shortness of breath, obstruction in asthmatic patients and fibrosis, So it is a good indicator for allergic diseases [43]. This result was in agreement with the results in Iraq, Al-Quraishi [34] who found that the IL-18 level in serum was significant increase as compared to control, and had a function in children asthma mechanism. The IL-18 and IL-18 receptor were highly expressed in asthmatic patients [44].

Junling [46] studies they regarded that the IL-18 was significantly increase in asthmatic children patients, linked with severity of asthma and may have a major role in atopic asthma. Some study reported the IL-18 expression in higher level in asthmatic patient as compared to control [45]. Kawayama [18] reported that there were significantly increase in serum level IL-18 in asthmatic and rhinitic patients, and IL-18 can be use as a biological marker for allergy diagnosis, While Cebeci [47] who registered the IL-18 level was significantly low in kids with acute asthma. These increases in levels may be due to the role of IL-18 in allergic mechanism especially in activated B cells to produce IgE and differentiation of native T cell to Th1 and Th2.

REFERENCES

- [1] Douglass, J.A. and O'Hehir, R.E (2006). Diagnosis, treatment and prevention of allergic disease: the basics. *Med J Aust.*, 185(4):228- 33.
- [2] Yap, J.M.; Ching, M.W.; Cabanilla, C.Q. and Ramos, J.D. (2014). Multiple house dust mite allergens sensitization profiles in children with allergic asthma. *Journal of Allergy & Therapy*, 5:3.
- [3] Olin, J.T. and Wechsler, M.E.(2014). Asthma: Pathogenesis and novel drugs for treatment. *British Medical Journal*, 24;349:g5517.
- [4] Asthma (2015). Available online at: <http://www.who.int/mediacentre/factsheets/fs307/en/> (Accessed November 2013).
- [5] Vercelli, D.(2008). Discovering susceptibility genes for asthma and allergy. *Nat. Rev. Immunol.* 8,169–182.
- [6] Bush, R.K. and Peden, D.B.(2009). Advances in environmental and occupational disorders in. *J. Allergy Clin. Immunol.* 123,575– 578.
- [7] Gould, H.J. and Ramadani, F.(2015). "IgE responses in mouse and man and the persistence of IgE memory," *Trends in Immunology*, 36, (1), 40–48.
- [8] Dullaers, M.; De Bruyne, R.; Ramadani, F.; Gould, H.; Gevaert, P. and B. N.(2012). Lambrecht, "The who, where, and when of IgE in allergic airway disease," *Journal of Allergy and Clinical Immunology*, 129(3) :635–645.
- [9] Eigenmann, P. A.; Atanaskovic-Markovic, M.; Hourihane, J. O'B; Lack, O.B; Lau; Matricardi, P. M.; Muraro, A.; Namazova Baranova, L.; Nieto, A.; Papadopoulos, N. G.; Rethy, L.A.; Roberts, G.; Rudzeviciene, O.; Wahn, U.; Wickman, M. and Host, A.(2013). Testing children for allergies: why, how, who and when. An updated statement of the European Academy of Allergy and Clinical Immunology (EAACI) Section on Pediatrics and the EAACI-Clemens von Pirquet Foundation. *Pediatric Allergy and Immunology*, 24(2) :195–209.
- [10] Pete, S.(2015). Triggers of allergic rhinitis: Inhalant allergens. *Global Atlas of Allergic Rhinitis and Chronic Rhinosinitis*. 116-118.
- [11] Platts-Mills, T.A.E.; Adkinson, N.F.; Bochner, B.S.; Busse, W.W.; Holgate, S.T.; Lemanske, R.F. and Simons, F.E.R.(2009). Indoor allergens. In: Middleton's Allergy, Principles and Practice Edition 7. Mosby Elsevier; :539–55.
- [12] Thomas, W.R.(2012). House dust allergy and immunotherapy. *Hum Vaccin Immunother*, 8:1469-1478.
- [13] Wood folk, J.A.(2005). Allergy and Dermatophytes. *Clin Microbiol Rev* 18:30–43.
- [14] Corren, J.; Lemanske, R.F.; Hanania, N.A.; Korenblat, P.E.; Parsey, M.V.; Arron, J.R.; Harris, J.M.; Scheerens, H.; Wu, L.C.; Su, Z.; Mosesova, S.; Eisner, M.D.; Bohen, S.P.; Matthews J.G. and Lebrikizumab. (2011). treatment in adults with asthma. *N Engl J Med*, 365: 1088-1098.
- [15] Wynn, T.A. (2003). IL-13 effector functions. *Annu Rev Immunol* 21:425–456.
- [16] Gabriele, G.; David, B.; Joan, R. and Marsha, W.(2012). Interleukin 13 and the evolution of asthma therapy. *Am J Clin Exp Immunol.*; 1(1): 20–27.
- [17] Junttila, I.S.; Watson, C.; Kummola, L.; Xi, C.; Jane, H.L.; Liying, G.; Ryoji, Y. and William, E. P.(2013). "Efficient cytokine induced IL13 production by mast cells requires both IL33 and IL3," *Journal of Allergy and Clinical Immunology*, 132, (3) : 704–712.

- [18] Kawayama, T. ; Okamoto, M. ; Imaoka, H. ; Kato, S. ; Young, H.A. and Hoshino ,T.(2012). "Interleukin18 in pulmonary inflammatory diseases," *Journal of Interferon and Cytokine Research*, 32, (10) : 443–449.
- [19] Cohn, L. ; Elias, JA. and Chupp, GL.(2004). Asthma: mechanisms of disease persistence and progression. *Annu Rev Immunol*,22:789-815.
- [20] Ying, L.u. ; Jiqian, F. ; Lu, T. and Huajin (2015).Advanced Medical Statistics. 2 nd Edition.
- [21] Rasheed, S.M.H. (2016).Role of Total and Specific IgE in Identification of Inhalant Allergens and their Association with HLA-DRB1 Alleles in AL-Najaf province. University of Kufa. *Journal University of Kerbala*, Vol. 14 No.4 Scientific . /College of Medicine.
- [22] Brakhas,S.A.; Atia,M.R.; Aziz,Y.J. and AL- Sharqi,S.A.H. (2015). Study of total IgE levels and eosinophil count according to age and gender in patients with allergic rhinitis. *World J Pharm Res.*, 4(1):295-303.
- [23] Wahhab, R.S.(2013). Investigate Role of IL-17 and Its Relationship Some Immunological Indicators and Severity in Patients of Allergic Asthma, AL-Mustansiriya University ,College of Basic Education.
- [24] Baldo,B. A. (2014). IgE and Drug Allergy: Antibody Recognition of 'Small'Molecules of Widely Varying Structures and Activities. *Antibodies*,(3):56-91.
- [25] Desa, M. and Dasilva, A. (2015). Specific IgE test: Size, age and pathologies that most require thus test in Northeastern city of Brasil. *Allergy Organization Journal*, 8:(1):244.
- [26] Ziętkowski, Z. ; Dolińska, C. ; Ziętkowska, E.and Bodzenta-Łukaszyk, A.(2013). The analysis of several patogenetic and clinical paramethers among patients hospitalized due to asthma. *Prog Health Sci* 2013, No1 Analysis patogenetic clinical paramethers patients hospitalized asthma. Vol. 3(1) : 19-27.
- [27] Manohar, S. and Selvakumaran, R. (2012). Estimation of serum immunoglobulin E (IgE) level in allergic asthma and allergic rhinitis patients before and after treatment. *European Journal of Experimental Biology*, 2(6):2199-2205.
- [28] Couto, T.A.; Falsarella, N.; Mattos, C.D. and Mattos, L.C. (2014). Total IgE plasma levels vary according to gender and age in Brazilian patients with allergic rhinitis. *Clinics*, 69(11):740-744.
- [29] Rasheed, S.M.H. ; Safaa, A. K. and Sabah, N. AL-Fatlawi.(2014). Results of Serum specific IgE (ssIgE) allergy test in adult patients suffering from respiratory allergy in Al-Najaf City.
- [30] Alwan, A.H. and AL-Dulaimy, R.A. (2011). Study of skin sensitivity to various by prick skin test in patients with bronchial asthma. *Diyala Journal of Medicine*, 1(2):78-82.
- [31] Moitra, S.; Sen, S.; Datta, A.; Das, S.; Das, P.; Biswas, S. and Bandyopadhyay, S. (2014).Study of allergenicity spectrum to aero allergens by skin prick testing. *Austin Journal Allergy*, 1(1):4.
- [32] Lokaj-Berisha, V.; Berisha, N.; Lumezi, B.; Ahmetaj, L.; Bejtullahu, G.; Karahoda, N. and Pupovci, H. (2012). Sensitization to aeroallergens in patients with respiratory allergies based on skin prick test results. *Iranian Journal Public Health*, 41(10):29-35.
- [33] Assarehzadegan,M.A.;Shakurnia,A.H and Amini,A.(2013). Sensitization to Common Aeroallergens among Asthmatic Patients in a Tropical Region Affected by Dust Storm. *J Med Sci* . 13: 592-597.
- [34] Al-Quraishi G. M.(2013). Serum Levels of Total IgE, IL-12, IL-13 and IL-18 in Children Patients with Asthma. *Iraqi J Pharm Sci*, Vol.22(1).
- [35] Wioletta, Z. ; Katarzyna, G. ;Marek, K. ; Maciej, S. and Tomasz, G.(2014). Nitric oxide, IL-6 and IL-13 are increased in the exhaled breath condensates of children with allergic rhinitis. 2013 Foundation *Acta Pædiatrica*. Published by John Wiley & Sons Ltd , 103 : e148–e153.
- [36] Panaitescu, C. ; Laura, M. and Luminita, C.(2014).Influence of Interleukin-4 and Interleukin-13 on serum immunoglobulin E in house dust mite allergy. *Clinical and Translational Allergy*, 4(2):P22.
- [37] Wang, X. ; Ma, C.; Zhang, Y. ; Ning , L. ; Chen, H and Zhou, F.(2013). Clinical Significance of the Dynamic Changes in Serum Eotaxin, Interleukin 13 and Total IgE in Children with Bronchial Asthma. *Iran J Pediatr Oct*; Vol 23 (5): 525-530.
- [38] Lee, J.S. ; Rosengart, M.R. ; Kondragunta, V.; Zhang, Y. ; McMurray, J. ; Branch, R.A ; Augustine, M.K. ; Choi and Sciruba, F.C.(2007). Inverse association of plasma IL-13 and inflammatory chemokines with lung function impairment in stable COPD: a cross-sectional cohort study. *Respir Res*. 8:64.
- [39] Gauvreau, G. ; Louis-Philippe, B. ; Donald, W. ;Cockcroft, J.; Mark, F. ;Chris, C. ; Beth, E. ; Davis , Francine, D. ; MyLinh, D. ; Billie, L.; Durn , Karen, J.; Howie , Linda, H. ; Marion; Kasaian, T. Kieran, J. K. ;Tara, X. ; Strinich , Richard, M. W. ;Nathalie, Y. ; Simon, Z. ; Donald, R. and Paul, M. O'Byrne .(2011). Effects of Interleukin-13 Blockade on Allergen-induced Airway Responses in Mild Atopic Asthma. *Am J Respir Crit Care Med* , 183: 1007–1014.

- [40] Farrokhi, S.; Gheybi, M.K.; Movahed ,A.; Tahmasebi, R. ; Iranpour, D. Fatemi, A.; Etemadan, R.; Gooya,M.; Zandi,S. ; Ashourinejad,H.; Alavizadeh,S. and Khoddami, S.(2015).Common Aeroallergens in Patients with Asthma and Allergic Rhinitis Living in Southwestern Part of Iran: Based on Skin Prick Test Reactivity. Iran J Allergy Asthma Immunol.14(2):133-8.
- [41] Adjers, K.; Luukkainen, A. ; Pekkanen, J. ; Hurme, M.; Huhtala, H.; Renkonen, R. ; Wang, Y.; Mäkelä, M.J. ; Karjalainen, J.; Toppila-Salmi, S.; (2017).Self-Reported Allergic Rhinitis and/or Allergic Conjunctivitis Associate with IL13 rs20541 Polymorphism in Finnish Adult Asthma Patients.Int Arch Allergy Immunol, 172(2) :123-128.
- [42] Kuperman, D.A. and Schleimer, R.P.(2008). Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. Curr Mol Med; 8: 384–92.
- [43] Wynn, T.A. (2003).IL-13 effector functions. Annu Rev Immunol 21:425–456.
- [44] Oda, H. ; Kawayama, T. ; Imaoka, H. ; Sakazaki, Y. ; Kaku, Y. ; Okamoto, M. ; Kitasato, Y. ; Edakuni, N. ; Takenaka, S. ; Yoshida, M. ; Iwanaga, T. ; Kato, S. ; O'Byrne, P. and Hoshino, T. (2014). “Interleukin18 expression, CD8 T cells, and eosinophils in lungs of nonsmokers with fatal asthma,” Annals of Allergy, Asthma and Immunology, 112 (1) : 23–28.
- [45] Rachmid,M.; Bloch,O.; Shaul,A.A.; Ben-Yehudah, G. ; Bistritzer, Z. ; Weintrob, N. ; Ofan, R. and Rapoport, M.J.(2011). Young patients with both type 1 diabetes mellitus and asthma have a unique IL-12 and IL-18 secretory pattern. Pediatric Diabetes., Nov; 12(7): 596-603.
- [46] Junling,W. ; Huiyun, Z. ; Wenjiao, Z. ;Hua, X. ; Hongling, Y. ; Xiaoping, L. and Shaoheng, H.(2016). Correlation of IL-18 with Tryptase in Atopic Asthma and Induction of Mast Cell Accumulation by IL-18. Hindawi Publishing Corporation ,Mediators of Inflammation Volume, Article ID 4743176, 14 pages.
- [47] Cebeci, AN. ; Nuhoglu, Y. ; Arslanoglu, I. ; Erguven, M. and Agachan, N.(2006). The role of IL-18 in Th1/Th2 balance in children. Allergy Asthma Proc., 27:365–370.