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Review Article

Cytokine Patterns in Iranian Patients with Asthma

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Abstract

Asthma is one of the most common respiratory diseases caused by chronic airway inflammation. A complex network of cytokines could affect asthma development. IL-4, IL-13, IL-17, and IL-33 have been identified as cytokines associated with asthma severity and these cytokines can be considered as candidate biomarkers for predicting the asthma severity while the IL-10 is lower in asthmatics compared with healthy subjects. There are many controversies about the IL-22, IL-25, and TGF-β levels between the Iranian publications. No significant differences have been observed between the healthy subjects and the asthmatic cases regarding the IL-6 and IL-8.

Keywords: Cytokine; Level; Asthma; Biomarker; Iran

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Introduction

Asthma is one of the most important chronic respiratory diseases that causes sporadic breathing difficulties. It is associated with the airway hyper-responsiveness that leads to recurrent episodes of wheezing, breathlessness and coughing (1). According to the recent studies, it affects more than 340 million people worldwide (2). In Iran, the prevalence of the asthma was reported at about 5.7-10.5% and 4.3-8.8%, among the adult and children population, respectively (3, 4).

It has been shown that a complex network of cytokines, plays an important role in the asthma pathogeneses (5, 6). T helper (Th) 2-related interleukins (IL) include the IL-2, IL-3, IL-4, IL-5, IL-7, IL-9, IL- 15, IL-16, and IL-17, that have been recognized as a key participant in the pathophysiology of the asthma to date (7). Besides, none-Th2 related cytokines, including the pro-inflammatory (IL-1, IL-6, IL-11, Granulocyte-Macrophage Colony-Stimulating Factor [GM-CSF]and the Tumor Necrosis Factor [TNF]) and

the inhibitory cytokines (IL-10, IL-12, IL-18 and interferon gamma [IFN-γ]) have been found to play an important role in the asthma progression and inhibition, respectively (7).

Asthma can be divided into the intermittent, mild, moderate, and severe stages, based on the pathogenesis, the degree of the airway obstruction and the responses to medication (8). Many studies, have evaluated the association between the cytokine profiles and clinical features of the asthmatic patients in different populations (9-11). Characterization of the cytokine profiles, might be a useful mean for developing a diagnostic biomarker for both treatment and management of asthma (12). In this study, we aimed to review the cytokine profiles in the asthmatic patients related to the disease severity, for identifying the appropriate cytokine biomarkers among the Iranian populations.

Cytokine Levels in the Iranian Asthmatic

As resumed in **Tables 1** and **2**, a total of 11 studies assessing the cytokine expressions or/ and cytokine levels in the Iranian asthmatic adults, were identified. The current study, aimes to disclose the role of cytokines and their associations with the asthma severity in the Iranian adult population, for the identificationof useful biomarkers.

IL-4

All studies performed on the Iranian population, have shown an increased level of IL-4 in the asthmatic subjects compared to the non-asthmatic ones (13-16).Two studies have reported an increased IL-4 level associated with the asthma severity (**Table 1**) (14, 16). Also, a positive correlation between the IL-4 gene expression and the serum IgE level was reported by Tavakkol Afshari et al (**Table 1**) (13). The increased IL-4 level among the iranian asthmatic population is similar to other countries (24, 25). Its increase is reasonable, because the IL-4 is an upstream cytokine that plays a key role in the allergic inflammation, by promoting the Th2 cell differentiation and the IgE production (26). Also, the IL-4 rise, is associated with the increased IgE level and is compatible with the hypothesis, that the maintenance of an increased IgE in patients with asthma is related to the IL-4 level (13, 27).

IL-13

The IL-13, is another important mediator of asthma, that operates many physiologic and pathological features of asthma. Increased levels of this cytokine in the sputum and bronchial biopsy specimens, are documented as features of severe asthma (28). There are limited data in the literature regarding the role of this cytokine in asthma in the Iranian population. A study was conducted by Tavakkol Afshari et al in the northeast of Iran, showed a higher expression of the IL-13 gene in the Peripheral Blood Mononuclear Cells (PBMCs) of the asthmatic patients compared to the healthy subjects (**Table 1**) (13). In this study, there was no correlation between the IL-13 mRNA gene expression and the IgE serum level. Both the IL-4 and IL-13 have been confirmed as a valuable biomarker for the Th2 inflammation in asthma (29).

IL-17

The IL-17 contributes to the asthma pathogenesis by inducing airway remodeling in addition to the inflammatory effects (30). Three studies among the adult population, showed the high IL-17A levels in the asthmatic patients compared to the healthy subjects (17-19). Elevated levels of the IL-17 were associated with the asthma severity (**Table 1**) (18, 19, 31). These results are consistent with other studies that have investigated the IL-17 role worldwide (10, 32). Regarding its relationship with the asthma severity, it has been proposed as an appropriate biomarker for the asthma severity and exacerbation (12). The IL-33 represents one of the vital important signals for the bronchial epithelial cells, that causes the development of asthma and has shown to be significantly correlated with the asthma severity (33, 34). Correlation of the IL-33 elevation with the asthma severity has been confirmed by studies in both children (35) and adults' (**Table 1**) (20) asthmatic cases in Iran, that is similar to other countries (36-39). Therefore, this cytokine has the potential to be used in the clinic to predict the asthma severity.

IL-10

In contrast to cytokines that increase the probability and severity of asthma, there are some cytokines whose expressions have a

Table 1. Cytokines related to asthma in the Iranian population

Cytokine	Study	Size	Laboratory test	sample	Results
IL-4	Tavakkol Afshari et al [13]	20/26[1]	RT-PCR ELISA	PBMC, Serum	Increase the expression of IL-4 gene and the level of serum IL-4 in asthmatic patients.
	Saba MA et al [14]	110/70[1]	ELISA	Serum	Increase IL-4 level with increasing asthma severity.
	Hoseini-Shahrestanak S [15]	30/36[1]	RT-PCR ELISA	Serum, PBMC	Increase IL-4 level in the serum level and PHA-stimulated PBMCs in asthmatic patients.
	Mosayebian A et al [16]	37/32[1]	ELISA	PBMC	Increase IL-4 level with increasing asthma severity in stimulated PBMC.
IL-13	Tavakkol Afshari et al [13]	20/26[1]	RT-PCR ELISA	PBMC	Increase IL-13 gene expression in 70% of patients with allergic asthma.
IL-17	Mowahedi M et al [17]	110/81[1]	ELISA	Serum	Increase IL-17A level and IgE concentration in patients with asthma.
	Sherkat R et al[18]	23/23[1]	RT-PCR Flow-cytometry	PBMC, Sputum	Increase IL-17 mRNA expression with increasing disease severity. Increase IL-17 level in serum samples in comparison to sputum.
	Zonoobi E et al [19]	27/26[1]	RT-PCR	PBMC	Increase IL-17 mRNA expression in severe asthma in comparison to control. A significant correlation between IL-17 level and asthma severity.
IL-33	Momen T et al [20]	89/57[1]	ELISA	Serum	Increase IL-33 level with increasing disease severity. A significant direct association of IL-33 with age and with total IgE level in the asthmatic group.

IL, interleukin; RT-PCR, real time-polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; PBMC, peripheral blood mononuclear cell; PHA, phytohaemagglutinin.
[1]Asthmatic/Control

Table 2. Cytokines related to asthma in the Iranian population

Cytokine	Study	Size	Laboratory test	Sample	Results
IL-22,25	Nadi E et al [21]	21/20[1]	ELISA	PBMC Serum	No significant difference between asthmatic and non-asthmatic subjects.
	Sherkat R et al [18]	23/23[1]	RT-PCR Flow-cytometry	PBMC Sputum	Increase IL-22, 25 levels with increasing disease severity. The increase is higher in serum samples than sputum sample.
IL-10	Zonoobi E et al [19]	27/26[1]	RT-PCR	PBMC	Decrease IL-10 levels in severe asthma patients in comparison to healthy subjects.
TGF-β	Ghanei M et al [22]	29/16[2]	Semi-quantitative PCR	Sputum	Decrease TGF-β expression is associated with well-pulmonary function status.
	Hoseini-Shahrestanak S et al [15]	30/36[1]	RT-PCR ELISA	Serum PBMC	Increase TGF-β level in serum, non-stimulated and stimulated PBMCs in patients with increasing asthma severity.
IL-6, IL-8	Ghaffari J et al [23]	21/30[3]	ELISA	Serum	There is not any difference between severe and mild asthma in serum IL-8 and IL-6.

IL, interleukin; RT-PCR, real time-polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay; PBMC, peripheral blood mononuclear cell.
[1]Asthmatic/Control; [2]Asthmatic/COPD ; [3]Sever/Mild asthma

reverse association. The IL-10 is known as the most important agent in the resolution of inflammation in asthma (40). Compared with the health control, a decreased serum level of the IL-10 has been reported in the asthmatic patients in Iran (**Table 2**). Consistent with some other

published international cohorts (19, 39, 41, 42), while it's up-regulation has been shown in few studies (43, 44). The decreased IL-10 level, may be due to the impaired IL-10 production from the T cells in asthma and also, autoregulatory IL-10 can be produced after allergen challenge by macrophages (45). Also, an IL-10 promoter polymorphisms (46), and reduced IL-10 effector functions in the atopic asthmatic subjects were reported.

IL-22, 25

Results of the available studies showed controversies regarding the role of the IL-22, IL-25, and Transforming Growth Factor beta (TGF-β) data in the Iranian asthmatics patients. Likewise, the function of these cytokines in respiratory inflammation, has not been completely identified in the other international studies. The IL-22, has both the inflammatory and anti-inflammatory properties (47). There is no similar pattern for the IL-22 levels in Iranian and other studies worldwide. It was reported that, the increased IL-22 concentration was related to the disease severity (48) that is parallel to the Sherkat et al. results in Isfahan, Iran (18). However, Nadi et al in the neighborhood province, Hamedan, showed no significant differences of this cytokine between the asthmatic and healthy population (**Table 2**) (21). The IL-25 cytokine, has a critical role in the asthma development through the IL-4 induction and Th2 polarization. It has been shown that the expression of this cytokine and it's cognate receptor, IL-17RB/RA, is significantly up-regulated in the asthmatic patients after the allergen challenge (49, 50), which is similar to Sherkat et al in Iran (**Table 2**) (18). On the other hand, Nadi et al, showed no significant difference in the IL-25 concentration between the asthmatic patients and the control group (**Table 2**) (21).

TGF-β

Also, inconsistent findings for the TGF-β, have been documented among various populations in Iran. However, the role of this cytokine in the asthma pathogenesis has been contentious owing to its complex signaling pathways and immune interactions, that affect different asthma phenotypes. The TGF-β restricts the inflammation by inducing the regulatory T cell differentiation, which in turn, inhibits the lung eosinophilia and the Th-2 and Th-1 infiltration. Moreover, it has a critical role in the asthma inflammation, by activating the inflammatory cells such as macrophages. The active TGF-β, is found to be increased in the bronchoalveolar lavage fluid and bronchial biopsy samples taken from the subjects with asthma (9, 51). This notion is compatible with the Hoseini-Shahrestanak et al's study in the southeast of Iran, which reported the high serum levels of this cytokine in the asthma patients that were associated with the disease severity (**Table 2**) (15). However, a reduced TGF-β level has been reported in the sputum of the asthmatic subjects by Ghanei M et al in Iran (**Table 2**) (22), that is consistent with Ling et al. who has reported a decreased expression in the TGF-β in the asthmatic airway epithelial cells (52). These contrasting results might be due to the various factors involved in the studies such as, different populations or methodologies. Asthma, as a complex and multifactorial inflammatory disease, may be affected by both the environmental and genetic factors. The gene-environmental interaction, has an important role in asthma (53). The environmental risk factors, are often complex and include respiratory infections, allergens, air pollution, cigarette smoke, dietary, medication, lifestyle, emotions and psychosocial factors that may affect the cytokine gene expression in asthma. In addition, geographical variation may contribute to the development of asthma and also affects the cytokine expression patterns among different populations (54). However, the methodological variations in diffrent studies, such as the sample size, state of disease in the studied patients, treatment strategies, evaluated tissue, method sensitivity and specification, may lead to the different cytokine expression patterns in varied studies.

IL-6, 8

No significant differences in the IL-6 and IL-8 levels between the asthmatic and non-asthmatic subjects, have been recognized for asthma in Iran (**Table 2**) (23), which are inconsistent with the other studies worldwide. Some studies, have shown elevated levels of the IL-6 and IL-8 cytokines in the asthmatic subjects (11, 55) and have considered the both cytokines, as the

inflammatory biomarkers for asthma.

Conclusion

In summary, this review indicated that, the increased IL-33, IL-17, IL-13, and IL-4 levels, are associated with the asthma severity among the different Iranian population. These cytokines can be used as a biomarker for predicting the asthma exacerbation. The genetic and environmental factors and diffrent methodology, may affect the cytokine patterns in asthma amongst different populations.

Conflict of interest

The authors declare that there is no conflict of interest.

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