



THE ESTIMATION LEVELS OF IL-6 AND IL-18 AS INFLAMMATORY BIOMARKERS IN OBESE AND NON OBESE PATIENTS WITH ALLERGIC RHINITIS

Naghm Yahia Ghafil¹, Sami Raheem Al-Katib², Yasir Lafta Hassoun³ and Seenaa Taqi Mansour⁴

^{1,2}Department of Medical Physiology, Faculty of Pharmacy, Kufa University, Iraq

³Department of Otolaryngology, Faculty of Medicine, Kufa University, Iraq

⁴Department of Biology, Faculty of Pharmacy, Kufa University, Iraq

Email : mohammad.hasan2013@yahoo.com

Abstract

The objective of the present study was to estimate level of IL-6 and IL-18 as inflammatory biomarkers in obese and non obese patients with allergic rhinitis (AR). The study population included 150 males and females patients with allergic rhinitis, their mean age was 30.733±10.95 years, they randomly recruited from the department of otolaryngology/ENT-clinic in Al-Sadder teaching hospital in AL-Najaf AL-Ashraf government during the period from 2nd April 2016 to 30th March 2017. The patients were divided into normal weights' group (n=6), under weights' group (n=51), over weights' group (n=43) and obese group (n=50) depending on BMI category. The levels of IL-6 and IL-18 in serum were measured by using ELISA-kit technique after complete clinical diagnosis and anthropometric measurements. The statically analysis of this study showed a significant increment ($P \leq 0.05$) in mean of IL-18 for overweight, obese patients and decline for underweight patients as compared with normal weight patients. Additionally, the results appeared a significantly differences in mean of IL-18 ($P \leq 0.05$) level in mild and moderate nasal smear eosinophilia when compared with normal eosinophils count in nasal smear. Also, the results showed no significant differences ($P \geq 0.05$) in mean of IL-6 among underweight, overweight and obese patients as compared with normal weight one and no significant differences in serum level of IL-6 among mild, moderate and severe eosinophilia as compared with normal eosinophils count in nasal smear. Separately from BMI, there were no significant differences in mean of IL-6 and IL-18 with various age groups. This study concluded that over weight and obese patients with allergic rhinitis were associated with significant high serum level of IL-18 along with eosinophilia as manifested by elevated IL-18 level in high grade of eosinophilia in nasal smear.

Keywords : Biomarkers, eosinophilia, IL-6, IL-18

Introduction

Allergic rhinitis is a soreness and inflammation of nasal mucosa when the immune system responds to aeroallergen, it considers a common public healthiness issue with an existing prevalence of more than 500 million individuals around the world (Wheatley and Togias, 2015). The sensitivity to indoor and outdoor allergens can occur between age 2-4 years while appearance of symptoms occurs around 9 years, the incidence of AR occurs between twenty and forty years and it increases in Gulf and Near East countries (Joseph *et al*, 2016). Allergic rhinitis considers a risk factor for the development of bronchial asthma and its occurrence ranges from 10-40% in rhinitis patient, AR is a stimulating factor for exacerbation secretion of pro-inflammatory cytokines and recruitment of eosinophil into nasal mucosa and lavage fluid during asthma so that, active early treatment of AR have appreciated effect on preventing of existing asthma and other comorbidities (Maureen-Supinda, 2015).

Obesity is considered a low-grade inflammation of white adipose tissue resulting from chronic activation of the innate immune system; adipocytes share with macrophage similar complement activation and production of pro-inflammatory IL-6 and IL-18 cytokines (Kiguchi *et al*, 2009). Several studies proved that obese individuals are more vulnerable to allergy, obesity appears to be linked with the incidence of AR and it has an influence on the severity of AR. In addition to, some macrophages and fibroblasts and recently adipocytes are the major sources for circulating IL-6 (Yang *et al.*, 2016; Baines *et al.*, 2015).

Previous study found IL-6 has crucial role in differentiation of B-lymphocyte into IgE- synthesis cells and secretion of antibody, hence IL-6 increases through obesity due to high expression of IL-6 mRNA of secreting cell and

its elevated associated with increased risk of AR (Mihara *et al*, 2012).

IL-18 is created by macrophages and TH-1 cells, its production is early stimulated through inflammatory reaction and high expression of IL-18-alpha-receptor-mRNA on eosinophils through allergy (Yuan *et al.*, 2017).

Some studies established high level of IL-18 in nasal secretion through asthma, eosinophilic and rhinitis, it may effect on migration of eosinophils (Zhang *et al.*, 2011; Sanders-Mishra, 2016). However, the relation between level of IL-18 and AR is still debate

Materials and Methods

A cross-sectional study included 150 obese and non obese patients (male and female) with entire diagnosed by an otolaryngologist as allergic rhinitis, their aged between 15-60 years. All patients were selected accidentally through their attending to the department of otolaryngology/ ENT-clinic in Al-Sadder teaching hospital in AL-Najaf AL-Ashraf government through the period from April 2016 to March 2017. The inclusion criteria incorporated patients had no history of other type of allergic disease, cancer, inflammation and respiratory diseases were studied.

The questionnaire sheet was used for presenting information associated with patients' demographical characteristics such as age, gender, address and BMI; the personal history for allergic rhinitis like duration, type, non specific and nasal symptoms of rhinitis. On the other hand, the elimination criteria were included patients with alcohol intake, smoking history, asthma, atopic dermatitis, hyper IgE syndrome or any allergic skin disease, pregnant women and the patients who had history of infectious or inflammatory diseases in the last two weeks or having used any

medications in the last week. The vocal approval was taken from all involving patients were exposed to similar procedure, they agreed to drawing venous blood sample (5ml) for measurement human serum level of IL-6 and IL-18 by using precise Enzyme Linked Immunosorbent Assay (ELISA) kits obtainable from manufacture company. The statistical investigation was completed by using SPSS (statistical package for social sciences) version 21. The data were presented as mean with standard error as descriptive statistics. Independent sample t-test and Chi square test for categorical data; p-value (≤ 0.05) regarded significant.

Results

A total 150 patients with allergic rhinitis had been concerned in this cross-sectional study, they were fifty obese and hundred non obese patients. The descriptive statistics for variables implicated in this study are appeared in table (1).

The evaluation of mean serum IL-6 and IL-18 levels among normal weight, underweight, overweight and obese patients with allergic rhinitis

The results indicated highly significant increment ($P \leq 0.05$) in mean of IL-18 for overweight and obese patients as compared with normal weight patients, while regarding the level of IL-6, the results shown no significantly

Table 1: Descriptive statistics of the variables for considered samples

Variables	Mean \pm SD	Range
Age in years	30.733 \pm 10.95	13-60
BMI Kg/m ²	27.383 \pm 5.213	14-40.2
IgE IU/ml	205.6 \pm 164.8	21.3-548
IL-18 pg/ml	72.411 \pm 46.42	12-210
IL-6 pg/ml	10.858 \pm 13.05	3.9-90.2

Table 2: Evaluation of mean serum levels of IL-6, IL-18 and IgE among normal weight, underweight, overweight and obese patients with allergic rhinitis

Variables	Normal weight (n=51)	Under weight (n=6)	Over weight (n=43)	Obese (n=50)
IL-6 pg/ml	14.07 \pm 1.08	15.73 \pm 2.7	14.07 \pm 1.23	16.70 \pm 1.24
IL-18 pg/ml	68.04 \pm 4.92	36.61 \pm 5.85 b	78.07 \pm 6.47 a	82.05 \pm 7.24 a
IgE IU/ml	224.1 \pm 21.66	385 \pm 55.02 a	222.78 \pm 23.3	167.9 \pm 24 b

(a)= indicate statically significant increased ($P \leq 0.05$) as compared with normal weight. (b)= indicate statically significantly decreased ($P \leq 0.05$) as compared with normal weight patients.

Table 3: Comparison of mean serum IgE, IL-6 and IL-18 levels with different age groups for patients with allergic rhinitis

Age	10-20 (n=30)	21-30 (n=51)	31-40 (n=42)	41-50 (n=21)	51-60 (n=6)	P value
IgE IU/ml	262.2 \pm 28	199.1 \pm 21.2	193.7 \pm 24.4	192.8 \pm 40.8	134.1 \pm 65.9	0.255
IL-6 pg/ml	15.79 \pm 1.2	14.10 \pm 1.1	15.33 \pm 1.16	17.45 \pm 2.5	16.31 \pm 2.96	0.619
IL-18 pg/ml	64.87 \pm 9.2	72.68 \pm 5.0	77.56 \pm 7.74	78.3 \pm 12.6	51.06 \pm 14.4	0.577

Table 4: Assessment of mean serum concentration of IgE, IL-6 and IL-18 according to grading frequency of nasal smear eosinophilia for patients with allergic rhinitis

Parameters	Normal eosinophilia (n=15)	Mild eosinophilia (n=58)	Moderate eosinophilia (n=40)	Sever eosinophilia (n=37)
IgE UI/ml	207.3 \pm 35.4	232 \pm 21.6	210.1 \pm 25	182.2 \pm 29.4
IL-6 pg/ml	15.7 \pm 1.03	15.4 \pm 1.14	14.9 \pm 1.2	14.08 \pm 1.46
IL-18 pg/ml	61.9 \pm 10.3	86.4 \pm 9.07a	80.6 \pm 7.11a	52.3 \pm 5.21

Discussion

Mean serum levels of IL-6, IL-18 and IgE with body weight and age

differences in mean of IL-6 among underweight, overweight and obese patient when compared with normal weight one as appeared in table (2).

Comparison of mean serum IgE, IL-6 and IL-18 levels with different age groups for patients with allergic rhinitis:

There were no significant differences ($P \geq 0.05$) between the different age groups (10-20, 21-30, 31-40, 41-50 and 51-60 years) with serum level of IgE, IL-6 and IL-18 for patients with allergic rhinitis as shown in Table (3).

The relationship between the grading frequency of eosinophils count in nasal smear and serum concentration of IL-6 and IL-18 for patients with allergic rhinitis:

There were significantly differences ($P \leq 0.05$) in mean of IL-18 for mild and moderate nasal smear eosinophilia when compared with normal eosinophils count in nasal smear for patients with allergic rhinitis while insignificant differences in mean of IL-6 as found in Table (4). Further assessment of grading of nasal smear eosinophils was achieved by using grading frequency that constituted from normal, mild, moderate and sever eosinophilia (Abhey, 2005).

The results agreed with *pfaar et al.* who found a significant decline level of IgE in underweight patient with allergic rhinitis in comparison with normal weight one (Pfaar et al, 2014). Since low leptin level in underweight patients induces synthesis a high amount of IgE in nasal mucosa, as

well as, it inhibits activity of IFN- γ from T-helper1 cells and increases T-helper2 cells production of IgE in response to allergen (Mohamed *et al.*, 2017), also in lean individuals, there is lofty numbers of tryptase mucosal mast cells that have great expression of high affinity Fc ϵ R1-IgE receptors and lead to creation more IgE from these cells higher than obese one and this consistent with previous study (Metcalf, 2008).

In addition to, the results of this study revealed a serum IL-18 level increment significantly with increasing body weight in both over weight and obese patients; these results reliable with prior study who established adipocytes and adipose tissue-containing macrophages in replying to immune reaction can produce additional amount of pro-inflammatory IL-18 through allergic rhinitis, huge quantity of fat and macrophages that contribute with high level of IL-18 can observe in obese subject (Nathan *et al.*, 2016).

As well as, these results agreed with concurrent study who hypothesized that high numbers of macrophages have the capability to produce cytokines stimulate differentiation and survival of T-helper1 cells to produce more IL-18 in overweight individual (Jun *et al.*, 2017). Besides, numerous studies simultaneous with these results, Tan *et al.* indicated that adipocytes secrete IL-18 but, in low quantity due to diminishing expression of IL-18-receptor mRNA on adipocyte in underweight patient (Tan *et al.*, 2010).

Moreover, serum level of IL-6 was insignificantly differences along with underweight, overweight and obese as compared with normal weight one and this consistent with cross-sectional study who found a steadiness in production of IL-6 occurred in different body weight due to activation of almost inflammatory cells and T-helper1 cells to produce inflammatory cytokine IL-6 in nasal mucosa and in circulation through allergic rhinitis (Rasoul *et al.*, 2014).

Regarding serum levels of IL-6 and IL-18, there were insignificantly differences with age groups and this agreed with earlier study who confirmed the detection of IL-6 in nasal mucosa and serum through early phase response of allergic rhinitis with various ages (Kirthana *et al.*, 2012). Also, serum IL-18 level increases through allergic rhinitis with different age groups and this approved with preceding study (Ariano *et al.*, 2003).

Mean serum IgE, IL-6 and IL-18 with grading frequency of nasal smear eosinophilia

The results of this study showed elevating IgE level in mild eosinophilia but it stills not markedly and this might due to sampling, demographical factors or when moderately numbers of nasal tissue eosinophils can produce their cationic proteins along with IgE synthesis in response to allergen and this agreed with parallel study (Rifat *et al.*, 2012).

Moreover, the level of IL-6 showed no differences among various grading of eosinophilia and this may possibly due to white adipose tissue-macrophages consider main source for more than 50% circulatory IL-6, in addition to, T-helper2 and leptin through their receptors can stimulate circulatory and tissue eosinophils to create IL-6 during allergy, IL-6 has little effect on migration of nasal eosinophils regard less gender and age but obesity is considered a risk factor for incidence of asthma and allergic

rhinitis and this approved with several studies (Peters *et al.*, 2016; Toshio *et al.*, 2014).

Serum level of IL-18 elevates in relative to severity of nasal eosinophilia, increment of IL-18 through perennial and seasonal rhinitis causes notable activation of T-helper cytokines to excite eosinophilic inflammation and its effect doubling in obesity and this agreed with concurrent study (Verhaeghe *et al.*, 2002). On the other hand, nasal epithelial cells produce high quantity of IL-18 in response to pollens, IL-18 motivates T-helper-IL-4 and IL-5 to cause chemo attractant of nasal eosinophils and this consistent with previous study (Yuriko *et al.*, 2006).

Allergic rhinitis was related with significant high serum level of IL-18 and there was obvious association between serum IL-18 and obesity as manifested by increasing severity of nasal eosinophilia along with elevating serum IL-18 and this is applicable weather in diagnosis or treatment of allergic rhinitis.

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