International Journal of Multidisciplinary and Current Research ISSN: 2321-3124
Research Article Available at: http://ijmcr.com

Evaluation of Leptin Hormone and Interlukin-18 levels in Patients with Seasonal Allergic Rhinitis

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Received 04 March 2018, Accepted 05 May 2018, Available online 08 May 2018, **Vol.6 (May/June 2018 issue)**

Abstract

Background: *Seasonal allergic rhinitis (SAR) is a familiar type of allergic rhinitis. It occurrs in a specific season when allergens "usually pollens" come directly in contact with nasal mucosa to cause IgE-sensitization in the early immune response stage. Profuse watery secretion, sneezing and itching are common symptoms involved in SAR. The recruitment and production of inflammatory macrophage and T cells- IL-18 and other cytokines are incorporated in delayed stage reaction. A pro-inflammatory adipose tissue adipokine-leptin is a strong stimulator for IL-18 secretion in female than male; IL-18 has an enormous inflammatory role by aggravating symptoms' severity during SAR.*
Study design: *A cross- sectional study.*
Aims: *To evaluate serum level of inflammatory leptin and its effect on IL-18 production, its level with IL-18 through SAR in comparison with perennial allergic rhinitis PAR, and to compare their values between male and female through SAR.*
Method: *One-hundred outpatients with SAR presented to the ENT-clinic with seasonal allergic rhinitis. Serum level of leptin, IL-18 and IgE antibody were examined by using ELISA-kit apparatus.*
Results and discussion: *There were significant differences in serum concentration of leptin for female as compared with male; there was an elevated IL-18 in proportion to leptin level which is an indicator for its secretion in female than male, there was significant differences in serum IL-18 in SAR as compared with perennial allergic rhinitis.*
Conclusion: *The serum level of leptin is an inducer for IL-18 production in female compared with male; high serum level of IL-18 through SAR might aggravate harshness of symptoms in certain season and these inflammatory markers could be useful as routine tests in assessing SAR.*

Keywords: *Seasonal allergic rhinitis, pollen, leptin, inflammatory cytokine-IL18, IgE, female*

Introduction

Allergic rhinitis (AR) is soreness and irritation of nasal mucous membrane as an immediate hypersensitivity reaction characterizes by periodic nasal secretion, sneezing and nasal obstruction. It can be classified depending on contact with indoor or outdoor allergen into *perennial* and *seasonal* allergic rhinitis (PAR) and (SAR) respectively (1). Seasonal allergic rhinitis is identified easily due to the commencement and offset of its symptoms occur rapidly in association with contact to spores and pollens; on the other hand, perennial allergic rhinitis is harder to determine and associated with further complex symptoms interrupted with recurrent upper respiratory tract infections and chronic sinusitis (2).

When the sensitizing allergen comes in attachment with nasal mucosa through SAR, it causes releasing of IgE from plasma cells which in turn, its stimulated degranulation of mast cells (3). The inflammatory mediators-derived mast cells affect capillary endothelial cells to augment expression of adhesion molecule on vascular cells for facilitating attachment of peripheral leukocytes with endothelial cells in late phase response of AR; the chemo attractant cytokines IL-4 promotes production of additional IgE from B-cells while IL-5 enhances infiltrating and recruitment of eosinophils, macrophage and T-lymphocytes into nasal mucosa to secret pro-inflammatory cytokines which result in mucosal inflammation, therefore, the nose becomes hyper responsive to different environmental irritants (4).

The detection of SAR is simple because of the prototype of symptoms are returned every year when expose to sensitize allergen, the effective common methods used for diagnosis of SAR are skin prick test and an allergy blood test; the blood test is quick and can be performed irrespective of skin condition or age and used

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DOI: https://doi.org/10.14741/ijmcr.v.6.3.3

to determine the level of specific and total IgE in serum by enzyme-linked immuno-sorbent assay (ELISA) and radio allegro sorbent test (RAST) apparatus, the total IgE-serum level more than 200U/I is considered as indicator for allergic individual (5). Leptin is adipokine secreted primarily from adipocytes of white and brown adipose tissue, ovaries and mammary epithelial cells; its receptors are located in arcuate nucleus of hypothalamus can help in regulation of food intake to accomplish energy homeostasis and its level increased parallel with body mass index and body fat store (6).

Numerous studies found an elevating serum leptin level in patient with SAR especially in female when compared with male patient and it depends on aeroallergen exposure, serum leptin in SAR should be estimated earlier to the beginning of use of anti-inflammation therapy (7,8).The quantity of white adipose tissue is increased in female more than male with the same body mass index and age, its characterized the chronic inflammation because of recruitment high numbers of macrophage in adipose tissue, stimulation of adipocytes and reactivation of pre-adipocytes to produce adipokine-leptin and inflammatory cytokines which typically drive immune system toward TH2- pattern (9).

The proinflammatory cytokine IL-18 or called interferon gama inducing factor and it is produced mainly by TH1 cells, dendritic cells and macrophage, IL-18 receptor belongs to IL-1 receptor family and it has α and β receptors; IL-18Rα is predominant and located on the surface of eosinophils, TH1 cells and macrophage which are stimulated through allergic inflammatory response to secret it. Also it involves in pathogenesis of metabolic disorder and its serum level elevated correspondingly with amount of adipose tissue due to the up regulation of gene expression of IL-18R and IL-18 protein on adipocytes of obese individual more than lean one and in female more than male (10 ,11).

Multiple studies demonstrated that many diverse polymorphism of IL-18 gene is associated with higher sensitization and risk of allergic rhinitis as well as, the serum concentration of IL-18 is remained higher in SAR even the exposure period for pollen is ended (12,13).

Leptin can play an important role in immune response. It enhances discharge of IL-18 from pro-inflammatory macrophage and TH1cells through allergic inflammation state (14). The classical pharmacological treatment of seasonal and perennial allergic rhinitis is dependent on the amount and duration of allergen-exposure and it involves oral second generation antihistamine and intranasal steroids " which reduces eosinophilia (15). Anti-inflammatory cytokine IL-37b isoform can bind with IL-18 receptor and IL-18 binding protein to block release of pro-inflammatory cytokine IL-18 can be a treatment model for patient with allergic rhinitis and help to reduce symptom's severity and may be beneficial to assessment patient with SAR clinically (16).

Patients and methods

This cross- sectional study had been performed in Al-Sader teaching hospital in Najaf/ Iraq during the period from April 2016 to March 2017. A total of 150 obese and non obese patients had been included; they were male and female outpatients recruited from the department of otolaryngology clinic and diagnosed by an otolaryngologist as allergic rhinitis , cases with no history of other type of allergic disease, cancer, inflammation and respiratory diseases were studied. Their aged between 15-60 years and their body mass index (BMI) around 14-40.2 kg/m^2. The prepared questionnaire was used for available information associated with allergic rhinitis patients' demographical characteristics such as (age, gender, address, job, and BMI); the personal history for allergic rhinitis such as duration, type, nasal and non specific symptoms of allergic rhinitis. The exclusion criteria were included the patients with smoking history, alcohol intake, asthma, atopic dermatitis or any allergic skin disease, hyper IgE syndrome, 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 venous blood sample (5ml) was received from each examined patient and put in a sterile plastic tube; placed in the centrifuge at speed 4000 rpm for about 6 minutes to isolate the serum which is put in epindroff tube and transport to biochemical laboratory for analysis by using enzyme linked immune sorbent assay (ELISA) kit obtainable from manufacture company to measure serum level of human pro-inflammatory interlukin-18, leptin hormone and the immunoglobulin-E (IgE).

Statistical investigation was prepared by using SPSS(statistical package for social sciences) version 20. The data were introduced as frequency with percentage and mean with standard error as descriptive statistics. Chi square test and independent sample t-test for categorical data; we put p-value ≤0.05 regarded significant.

Results

A total 150 obese and non obese patients with allergic rhinitis had been included in this study. They were 82 males and 68 females; their aged more than fifteen years and the descriptive statistics for particulars involved in the study are appeared in table (1).

Table 1: Descriptive statistics of the variables for studied samples

Variable	Mean ± SD	Range
Age in years	30.733±10.95	13-60
BMI Kg/m^2	27.383±5.213	14-40.2
Duration of allergic rhinitis in years	5.350±4.664	1-20
IgE IU/ml	205.6±164.8	21.3-548
IL-18 pg/ml	72.411±46.42	12-210
Leptin ng/ml	10.858±13.05	3.9-90.2

Table 2: Association between the gender and body mass index

		Gender		Total	P value
		Female	Male		
BMI Kg/m2	Under weight	1	5	6	0.274
		1.5%	6.1%	4.0%	
	Normal	21	30	51	
		30.9%	36.6%	34.0%	
	Over weight	19	24	43	
		27.9%	29.3%	28.7%	
	Obese	27	23	50	
		39.7%	28.0%	33.3%	
Total		68	82	150	
		100.0%	100.0%	100.0%	

Table 3: The assessment of total serum concentration of immunoglobulin-E, interlukin-18 and leptin hormone for male and female patients

Parameters	male (n=82) Mean±SE	female (n=68) Mean±SE	P value
IgE IU/ml	198.43±16.98	222.82±20.86	0.361
IL-18 pg/ml	64.99±3.02	77.29±4.93 a	0.030
Leptin ng/ml	6.39±0.54	14.07±2.21 a	<0.001

SE= standard error. (a)= indicate statically significant (P≤0.05) as compared with male patients

Table 4: Comparable values of serum level for immunoglobulin-E, interlukin-18 and leptin hormone between patients with seasonal and perennial allergic rhinitis

Variables	Patients with seasonal allergic rhinitis (n=94)	Patients with perennial allergic rhinitis (n=56)	P value
IgE IU/ml	207.43±16.84	205.58±21.10	0.946
IL18 pg/ml	77.95±3.09 a	63.09±3.30	0.029
Leptin ng/ml	9.25±1.180	11.01±2.14	0.435

a= indicate statically significant (P≤0.05) as compared with patients with perennial allergic rhinitis

The statiscal assessment showed that there is no significant differences with P value = 0.274 between body mass index category for 68 females with allergic rhinitis as compared with similar body mass index category for 82 males with allergic rhinitis as appeared in (Table 2).

In addition to, the results indicated that no statical significance with P value = 0.361 in serum concentration of IgE between male and female patients. The study found that higher statical significant (P≤0.05) in serum concentration of IL-18 and leptin hormone for female as compared with male patients with allergic rhinitis as showed in (Table 3). Furthermore, the results observed that serum level of IgE (P= 0.947) and leptin hormone (P= 0.435) were statically not significant between patients with seasonal and perennial allergic rhinitis. Similarly, the current study revealed that statically significant elevated (P=0.029) serum concentration of IL-18 for patient with seasonal allergic rhinitis as compared with patient with perennial allergic rhinitis as showed in (Table 4).

Discussion

Seasonal allergic rhinitis is a type of common instantaneous hypersensitivity reaction and it occurs when pollen and dust mite fecal protein are attached with nasal mucosa in definite season to develop IgE-dependent mechanism which stimulates degranulation of mast cells and basophils to produce inflammatory mediators in the early phase of response while IL-18 and other TH1-cytokines can enhance immune response and severe allergic inflammation (17).The pro-inflammatory IL-18 plays a major role in generation and maintenance of the inflammatory cascades through SAR. therefore, its measurement and subsequent management are the goals in declining its pathophysiological effects and modifying symptoms that affect on quality of life. (18).

In our study, 45% of patients were females and 55% were males and the results were of no statistical significance in regard to the body mass index for males as compared with females as appeared in (Table- 2), this finding is agreed with Violeta *et al*. who established no association between BMI and gender but there is increased prevalence of allergy with obesity due to its high leptin level (19,20).

In the present study, there is no significant differences (P≥0.05) in total serum concentration of IgE between males and females with allergic rhinitis (Table-3). This figure is consistent with Mallikarjun *et al*. who found elevated IgE level for SAR and PAR but not significant. This result may be due to an aeroallergen which is either allergic protein or antigen; antigens concerned are endotoxin, spores, dust, pollen and bacteria. They enhance plasma cells to produce IgE antibody that is not influenced by gender to initiate allergic reaction (21).

In addition to, this study shown a significantly elevated (P≤0.001) serum concentration of leptin hormone for female patients as compared with male patients with the same BMI (Table-3). Parallel finding is revealed by Erel *et al*. who stated that leptin secreted by adipocytes is of direct proportion with body fatty mass which is usually higher in female than male (22). Besides, Kalypso *et al*. estimated that the percentage of subcutaneous white adipose tissue in female is about 80% of total body fat stores while visceral adipose tissue in male accounts only 20% of total body fat with similar BMI, author contributed the results to the high gene expression on X-chromosome of female which is specially implicated in the control of amount and distribution of adipose tissue. (23).

The report by Yuntao and Qinghua affirmed that in female, the enlarged adipose tissue contain high numbers of infiltrating macrophage which is responsible for secretion of large quantity of pro-inflammatory cytokines IL-6 and tumor necrosis factor. Sadagurski *et al*. found that Leptin- isoform-b receptor is comparable structurally with IL-6 receptor and they are located on α neurons of hypothalamus; IL-6R within α neurons can have autocrine effect on Lepin-isoform-b by increasing the production of

STAT3 (signal transducer and adaptor trancrition-3) in hypothalamic which enhances expression of ob/ob gene of leptin that lead to high expression of leptin-mRNA transcription process and result in elevating serum concentration of leptin in female (24,25).

We found a significantly elevated (P≤0.05) serum concentration of IL-18 for female patients as compared with male (Table-3). Sanders and Mishra agreed with our study, they found a high serum concentration of IL-18 in female with allergic rhinitis compared with male independent on age and body mass index (26).

Numerous studies showed high expression of IL-18R.mRNA and IL-18R protein on adipocytes of subcutaneous adipose tissue in large quantity in female compared with male and they found an increase in numbers of inflammatory macrophages infiltrating adipose tissue of obese female more than obese male (27). A study by Ayse found that the secretion of adipokine leptin from white/ brown adipose tissue is always in direct positive correlation with allergic rhinitis' female (28). Leptin increases the proliferative activity of macrophage and T-lymphocyte in blood because their surfaces have high expression of leptin R-b isoform which in turn enhances the mRNA expression of caspase-1 (proteases enzyme) that consequently lead to conversion of pro-IL-18 to active form of IL-18 in circulation. also, leptin can stimulate T-cells propagation to produce additional IL-18 in circulation (29).

In the current study, the total serum concentration of IgE is significantly not different (P≥0.05) for patients with seasonal allergic rhinitis when compared with patients of perennial allergic rhinitis (Table-4), comparable findings are reported by Gameros *et al*. (30). Besides, our study showed statically no significant differences in serum level of leptin hormone between patient with SAR (11.01±2.14) and perennial allergic rhinitis (9.25±1.180), this figure may be attributed to serum leptin is frankly associated with quantity of body adipose tissue and elevated in female more than male and it's not affected via the type or amount of allergen exposure in SAR and PAR. This finding is consistent with report by Ciprandi *et al*. who found serum leptin level is depended on presence or absence of allergen or pollen in certain season or along the time and it is intensity increased in female than male (31). Moreover, the finding by Wenlong *et al*. publicized a strong relationship between higher serum leptin level and augmented incidence of SAR and PAR but statically no significant, its level is not affected by class and quantity of allergen in two types of rhinitis due to allergic reaction through rhinitis starts when indoor or outdoor allergen elicits nasal mucosa and not during secretion of leptin. However, leptin plays identical inflammatory task in seasonal and perennial allergic rhinitis by which it enhances accumulation and production of TH cells' pro-inflammatory cytokines (32). Furthermore, in this study, we found highly significant elevated serum concentration of IL-18 in patient with seasonal allergic rhinitis (77.95±3.09) as compared with perennial allergic rhinitis (63.09±3.30), this interesting figure might be atributed to the natural pollen-induced SAR is positively influencing the serum level of IL-18 more than mold or dust- causes perennial allergic rhinitis, this finding is agreed with the previous study by Kurt *et al*. who illustrated that serum level of IL-18 is elevated through seasonal allergic rhinitis and it is positively correlated with the quantity of natural pollen exposure-contact within nasal mucosa which stimulates pro-inflammation cytokine-IL18 production in chronic stage of seasonal allergic rhinitis (33). Besides, Hosoki *et al*. elucidated that hydrate pollen contains allergenic protein and secrets cysteine- serine proteases which causes oxidative stress to denderitic cells. NAD(P)H oxidases of intrinsic pollen enhances intracellular reactive oxygen species in epithelial cells which activates nuclear factor and MAPK- signaling pathway that are considered stimulators for transcriptional activator of chemokine-gene and up regulation of expression CD80and CD86 molecules in denderitic cells; they enhance secretion of IL-6 and IL-18. Also dendritic cells promote development of T-cells to produce IL-18 and other cytokines through SAR. (35).

Conclusion

Serum leptin is a powerful stimulator for secretion of IL-18 in female than male and it may be used in future to evaluate the symptoms' severity after pollen exposure in seasonal allergic rhinitis.The estimation of these inflammatory markers could be valuable test in assessing patients with SAR .

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