Asian Journal of Applied Sciences (ISSN: 2321 – 0893)
Volume 03 – Issue 05, October 2015

Elevated Body Mass Index and Serum Resistin are Associated with Severity of Allergic Rhinitis

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ABSTRACT— ***Background: Allergic rhinitis is a prevalent chronic respiratory problem that can impair quality of life, sleep and work. The increase in the prevalence of allergic rhinitis among the general population appears to have an association with weight. Obese individuals are more vulnerable to allergy. Resistin, a recently discovered adipokine, has been shown to have pro-inflammatory properties in humans. This study was designed to evaluate the body mass index of patients with allergic rhinitis and their serum resistin levels and to investigate their association with clinical disease severity.***
Methods: A case-controlled study was performed on 34 with persistent allergic rhinitis and 20 healthy controls with similar age and sex. Anterior rhinoscopy was done for all patients. Blood samples were collected from the patients for analysis including: total serum immunoglobulin E (IgE) cortisol and resistin. Each patient completed a questionnaire assessment to evaluate the severity of allergic symptoms including nasal obstruction, sneezing, rhinorrhea, and itchy nose. Height and weight were measured by a trained researcher.
Results: Body mass index and serum levels of resistin were significantly increased in patients with allergic rhinitis compared with controls, and both correlated positively with disease severity. In addition, they correlated positively with nasal symptom scores. A significant positive correlation was observed between serum levels of resistin with both IgE and body mass index.
Conclusions: Patients with allergic rhinitis persistent were found to have higher body mass index and serum levels of resistin, and their levels increased with the progress of disease severity. Resistin may represent a novel link between inflammation and allergic rhinitis .Weight control should be considered as a potential strategy to improve the health status of patients with allergic rhinitis, through the control of symptoms and the improvement of general health.

Keywords— allergic rhinitis (AR), body mass index(BMI), immunoglobulin E, total nasal symptom score (TNSS), resistin.

1. INTRODUCTION

Over the past decades, there is evidence that the prevalence of allergic disorders, such as rhinitis, has world widely increased in developed countries **[**1].Recent epidemiological and experimental data suggest that obesity might be linked to allergic sensitization. This association might involve common factors with regard to genetic disposition and environmental influences. [2] Several environmental factors have been hypothesized to be involved in the development

of allergic diseases; none could fully explain the rapid increase of the prevalence. However, some lifestyle factors, including dietary factors, alcohol consumption, physical inactivity, and obesity, have recently obtained distinctive regard. In addition, there is evidence that obesity and overweight are linked with allergic diseases probably because of the immunological effects of adipose tissue on development of allergies**.** [3]

Body mass index (BMI), measured in kg per square meter, is the most commonly parameter used to assess the excess of weight and obesity. Obesity and overweight is abnormal or excessive fat accumulation that may impair health and becoming a burden not only for affected patients but also public health systems. [4] Numerous epidemiological studies found a significant association between BMI and allergic disorders both in children and adults**.** [5] .
Allergic rhinitis is an IgE-mediated disease resulting in inflammation of the nasal mucosa **.[6]**The World Health Organization recommend classification of allergic rhinitis into two groups "intermittent" or "persistent" allergic rhinitis, instead of previous classification of "seasonal" or "perennial" allergic rhinitis.[7]

On exposure to an inciting allergen, inflammatory cells, including mast cells, CD4-positive T cells, B cells, macrophages, and eosinophils , infiltrate the nasal mucosa. The T cells infiltrating the nasal mucosa are predominantly T helper (Th) 2 in nature and release cytokines (e.g., interleukin [IL]-3, IL-4, IL-5, and IL-13) that promote immunoglobulin E (IgE) production by plasma cells. IgE production, in turn, triggers the release of mediators, such as histamine and leukotrienes, that are responsible for arteriolar dilation, increased vascular permeability, itching, rhinorrhea (runny nose), and mucous secretion. [8],[9]

Adipokine resistin is an adipocyte-secreted factor that is a member of low molecular weight cysteine-rich secreted peptides.It belongs to the family of resistin-like molecules**.**[10] Resistin is mainly expressed in monocytes, macrophages, spleen and bone marrow-derived cells, but is also expressed at very low levels in adipose cells.[11]

Resistin has been shown to have pro inflammatory properties[12].Resistin was demonstrated to modulate several molecular pathways involved in metabolic, inflammatory, and autoimmune diseases with possible roles for resistin in obesity-related subclinical inflammation, atherosclerosis and cardiovascular disease, rheumatic diseases, asthma and inflammatory bowel disease [13].According to studies in animals, resistin represents the link between obesity and insulin resistance[14].Therefore, this study was designed to evaluate the body mass index of patients with allergic rhinitis and their serum resistin levels and to investigate their association with clinical disease severity.

2. PATEINTS AND METHODS

This is a matched case-control study; thirty-four allergic rhinitis patients were enrolled in this study. In addition twenty healthy adult cross matched age and sex were taken as control group .Patients diagnosed with allergic rhinitis were enrolled from the outpatient clinics of the National Research Center (NRC) clinic, and ENT clinic, Alazhar University, Egypt during the period from July 2013 to March 2014. The diagnosis of allergic rhinitis was made according to the clinical manifestations and history. A written informed consent was obtained from each patient.

Exclusion criteria for this study were (1) Use of anti-allergic medications (antihistamine, decongestant, or topical steroids) within two weeks, (2) Patients under twelve years old, (3) Pregnancy and (4) Recent infectious condition.

Anterior rhinoscopic examination for all enrolled patients was done to establish the diagnosis and exclude local infection. Each enrolled patient completed a questionnaire assessment to evaluate the severity of symptoms within the latest 2 weeks: this questionnaire was specific to the severity of allergic symptoms including nasal obstruction, sneezing, rhinorrhea, and itchy nose. The symptoms were graded from 0 to 3 according to the severity within previous 2 weeks (0 = no symptom; 1 = mild symptom, no impact on daily life; 2 = moderate symptom, impact on daily life; 3 = severe symptom, impact on daily life).Body weight and height were measured by the researcher at the time respondents visited the clinic. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters (kg/m^2). The standard National Institutes of Health definition of obesity was used in assessing overweight or obesity among adults. Based on BMI, an individual was classified into normal (BMI ranged from 18.5 to 24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2), or obese (BMI $\geq$ 30 kg/m^2).Blood samples were collected from the patients at 9 a.m and the sera were separated in aliquots and preserved at -70 C° till the further biochemical analyses including: total serum immunoglobulin E (IgE), serum cortisol, and serum resistin.Serum cortisol level was determined according to the method of Bondy (1980)[15] using ELISA reagent kit purchased from Immunospect, Canoga Park, USA. Serum resistin level was measured using ELISA technique according to the method of De Luis and colleagues (2001)[16] using reagents of human resistin ELISA kit purchased from Biovedor GmbH, European Union, Germany. Serum immunoglobulin E (IgE) level was evaluated according to the method described by Michel and colleagues (1980)[17] using ELISA reagent kit purchased from Immunospect, Canoga Park, CA, 91303, USA. The obtained values were subjected to one way post Duncan Statistical Analysis of variance (ANOVA) test at $p<0.05$ using statistical analysis system (SAS) program software; copyright (c) 1998 by SAS Institute Inc., Cary, NC, USA. All data were presented as a mean± SD. Statistical

differences between values of patients and control groups were determined by student t- test. Comparison of qualitative variables among groups of subjects was made by the chi-square test. Mann-Whitney U test was used to examine possible differences in the severity level nasal symptoms where a normal distribution was not assumed. Correlation between the variables was performed by spearman correlation coefficient.

3. RESULTS

Both questionnaire assessment and anterior rhinoscopy were done for all patients, while measurement of BMI, serum IgE, resistin and cortisol levels were carried out for both patients and healthy subjects. The basic data of the patients enrolled in this study were listed in "Table 1.

There was no significant correlation between the allergic rhinitis patients' age, sex and smoking habit to the total nasal symptom scores (TNSS) or each symptom score. the BMI of all respondents ranged from17.70 to 46.41 kg/m2 and the mean BMI was 23.41 kg/m2 (SD 6.78). The mean BMI of females was 1.57 kg/m2 higher than males but it was not statistically significant (p = 0.116). Based on BMI, an individual was classified into normal (BMI ranged from 18.5 to 24.9 kg/m2), overweight (BMI 25-29.9 kg/m2), or obese (BMI ≥ 30 kg/m2).

Table 1: Mean levels of serum resistin (ng/ml), IgE (IU/l), and cortisol (µg/dl) in mild and moderate to severe allergic rhinitis patients as compared to normal control groups.

Parameters		Control n=20	Moderate-severe n=19	Mild n=15
Resistin ((ng/ml)		8.69 ± 1.04	18.88** ±1.86	10.85* ±2.58
IgE (Iu/l)		13±2.80	35.13***± 17.68	13.67s ±3.35
Cortisol (µg/dl)		13.1± 1.81	12.03 ± 2.00	12.27 ±1.37
Age (years)		29.57±11.26	31.37 ± 11.60	32 ± 10.41
Sex:	male	12(60%)	6 (17.64%)	9(60%)
	female	8(40%)	13 (38.24%)	6(40%)
Smoking	non	14 (75%)	16 (47.05%)	11 (73.3%)
	smoker	5 (25%)	3 (8.83%)	4(26.7%)

All data are expressed as mean ± standard deviation. * ($p<0.05$), ** ($p<0.01$) and ***. ($p<0.001$

The proportion of respondents with a BMI < 25 kg/m2 was 55.88% (n = 19) and the remaining 44.12% (n = 15) were those with a BMI ≥ 25 kg/m2. The proportion of overweight individuals was 26.5%; and 17.7% of respondents were obese. Due to the small sample size, respondents were commonly grouped into two groups, those who were not overweight or obese (BMI<25 kg/ m2) and those that were overweight or obese (BMI ≥ 25 kg/m2). In those classified as overweight or obese (BMI≥ 25 kg/m2), 43.75% were females and 44.45% were males. With a BMI cut-off point of 25 kg/m2, there was no statistical difference in BMI between males and females (p = 0.61)." Table 2 and "Table 3.

Table 2: The Body Mass Index of respondents.

	All	Males	Females
Mean	23.41	22.94	24.51
Median	22.16	21.31	23.12
Std. Deviation	6.78	4.42	5.98
Minimum	17.70	17.9	17.70
Maximum	46.41	38.25	46.41
Mean difference (p value)		1.9906 (p = 0.116)	

Mann-Whitney U test

Table 3: Prevalence of overweight and obesity in patients with allergic rhinitis

	Prevalence		
n (%)	BMI < 25	BIM 25- 29.9	BMI ≥30
Allergic rhinitis (34)	19 (55.8)	9 (26.5)	6 (17.7)
Control(20)	13 (65)	4(20)	3 (15)
By sex			
Females	9 (56.25)	4 (25)	3 (18.75)
Males	10(55.55)	5 (27.78)	3 (16.67)

3.1 Association between the severity levels of allergic rhinitis and body mass index

The type of analyses used to explore the association between the severity levels of AR and BMI: non-parametric (chi-square test).

3.2 Non-parametric analysis

BMI had a significant association with all AR symptoms. Individuals with a BMI ≥ 25 kg/m2 had six times greater risk of having more severe conditions of all AR symptoms (p = 0.023) than those with a BMI < 25 kg/m2.

Serum resistin level showed a significant increase in patients with mild allergic rhinitis (mean ±SD was10.85±2.58, P<0.05) and a highly significant increase in patients with moderate-severe allergic rhinitis (mean ±SD was 18.8±1.86, P<0.001).Moreover serum IgE level pointed only a highly significant elevation in patients with moderate-severe allergic rhinitis (mean ±SD was 35.13± 17.68P<0.001) matched with a non-significant elevation (p>0.05) regarding patients with mild allergic rhinitis. In contrast, serum cortisol level revealed non-significant reduction (P>0.05) in both patients with mild allergic rhinitis (mean ±SD was 12.27±1.37) and those with moderate-severe allergic rhinitis (mean ±SD was 12.03±2.00) respectively in compare to normal controls (mean ±SD was 13.1±1.81).Correlation demonstrated in table (4) between, concentrations of IgE, resistin and cortisol to the TNSS and each individual nasal symptom.

Table 4: Shows the correlation of serum resistin, IgE, cortisol levels and BMI with both individual nasal symptoms and TNSS in moderate, severe and mild allergic rhinitis patients.

	Resistin (ng/ml)	IgE (IU/l)	Cortisol (µg/dl)	BMI (kg/ m2)
Conges. and obstruct.	r = 0.395*	r = 0.329	r = -0.340	r = 0 .379*
Rhinorrhoea	r = 0.384*	r = 0.175	r = - 0.150	r =0.391*
Sneezing	r = 0.508**	r = 0.181	r = - 0.102	r =0.375*
Itching	r = 0.399*	r = 0.392*	r = 0.056	r =0.411*
TNSS	r = .736***	r = 0.490**	r = 0.165	r =0.386*
Resistin (ng/ml)		r =0.372*	r = -0.153	r =0.384*

(*P<0.05, **P<0.01 & ***P<0.001).

Serum levels of resistin,IgE, and BMI had significant positive correlation with the TNSS(P <0.001, P <0.01and P <0.05, respectively). When they go to the individual nasal symptoms, also they had significant positive correlation with the score of itchy nose(P <0.05) while serum resistin and BMI had significant positive correlation with the score of obstruction as well as the score of rhinorrhea (P <0.05) and high significant positive correlation with sneezing (P<0.01 and P<0.05, respectively).A significant positive correlation was observed between serum levels of resistin with both IgE and body mass index. Also, the obtained data proved that IgE levels had high significant correlation with the TNSS (r=0.490, p<0.001). When it goes to the individual nasal symptoms level, it had significant correlation with the score of itchy nose (r=0.399, p<0.05); while it didn't correlate with the other symptoms.

3.3 Limitations of the study

A small sample size may lead to some limitations in the application of quantitative analysis. Due to the small sample size, no stratified analysis was conducted. Finally, the measurements in this study were conducted at one point of time (cross sectional) and thus, the probability of recall bias was high.

4. DISCUSSION

Obesity and overweight is abnormal or excessive fat accumulation that may impair health and becoming a burden not only for affected patients but also public health systems. [4] Indeed, the increase in affluence, typical of western society, may result in increased availability of foods and decreased physical activities, both of them may contribute to promote the prevalence of obesity and overweight. Over the past decades, the prevalence of both obesity and allergic sensitization has been increasing in parallel in industrialized countries. [2]

Obesity has been associated with an increased risk of allergic disorders both in children and adults. [18], [19] However, the real association between obesity and allergic disorders is unclear.

As reported by several epidemiological studies, the prevalence of AR was slightly higher in males than females. In this study, the proportion of male and female respondents was almost equal (53% vs. 47%). This suggests that females may have the same risk as males in developing AR. Also the mean BMI of females with AR was 1.57 kg/m2 higher than males but it was not statistically significant (p = 0.116). With a BMI cut-off point of 25 kg/m2, there was no statistical difference in BMI between males and females (p = 0.61). [3] reported that the risk of allergic rhinitis increased with increasing BMI among women but not among men. Some studies reported a positive association between BMI and allergic disorders even if not consistent, mainly concerning the gender relevance. [20],[21]. But another study conducted on a large cohort of 1,247,038 Swedish military conscripts reported that obesity was not associated with allergic rhinitis in patients with nasal symptoms only. [21]

Studies assessing the association between AR and BMI have conflicting results. Several epidemiological studies showed a positive association between AR and high BMI. [22], [23], [24]whereas other studies reported that there was no association between AR and BMI .[25] Our study suggests that BMI was significantly associated with the severity of AR. Furthermore, it appears that obesity may be a potentially modifiable risk factor for AR, particularly relating to the severity of AR symptoms. Promoting healthy weight to patients with AR may have a favorable impact on controlling the severity of AR symptoms. However, further studies may need to be designed to investigate this issue further.

Adipokines are the proteins secreted by the adipose tissue involved in the regulation of the energy balance with the recently suggested putative role in allergic inflammation increasing the risk of asthma in obese individuals (Shore, 2007)[26].Resistin is an adipokine with proinflammatory properties in humans. In this study resistin has been analyzed in the serum of thirty-four patients with different degrees of allergic rhinitis and twenty healthy controls matched with the same age. The percentage of disease severity in adult allergic rhinitis was 15 (44%), mild, and 19 (56%), moderate–severe persistent allergic rhinitis. There were no significant differences in resistin concentration levels with sex distribution and mean values for age between allergic rhinitis and healthy controls.

Few studies have been conducted to verify a correlation between serum level of resistin and allergic rhinitis [5] .There was no significant correlation between the allergic rhinitis patients' age, sex and smoking habit to the TNSS or each symptom score that was in agreement with Hsueh and and colleagues.[27]

The results of the current study indicate a clear association between resistin level, BMI and TNSS and individual nasal symptom score, when comparing the severity of AR with serum resistin level, the results showed that the more severity of AR symptoms, the greater was the increased in BMI and serum resistin level. This was in agreement with some studies.[14], [22],[23],[24] who reported, in their studies, an increase in resistin levels in association with allergic disease severity; also agree with several epidemiological studies that showed a positive association between AR and high BMI; whereas other studies reported that there was no association between AR and BMI.[25]

AR, in particular, is a hypersensitivity reaction to specific allergens that occurs in sensitized patients, which is mediated by IgE antibodies that result in the inflammation. [28]

In the present study the serum level of IgE was significantly high in moderate-severe cases of AR patients than mild and control cases. In the same time, the high IgE level was highly significantly correlated with TNSS. When it goes to the individual nasal symptom levels it had significant correlation with the score of itchy nose, while it didn't correlate with the other symptoms. This result was in conformity with Marcucci et al. (2001)[29] where they correlated IgE levels to AR and reported that, the more sever of AR symptoms the higher was the IgE serum levels.

In the present study, there was a significant positive correlation between serum resistin level and serum total IgE. These finding was in accord with the study done by Kim and colleagues [30] which showed that resistin was positively associated with serum IgE. While, the results of the present study was contrary to Hsueh and colleagues. [27] that did not find a significant correlation between serum resistin and serum IgE levels.

In the present study, serum cortisol was recorded to be reduced in all patients with AR with different diseases stages .This result was in agreement with other studies [31]which stated that, morbidity of asthma and rhinitis were associated with reduced serum cortisol levels. In the present study, there were no correlations between TNSS, cortisol or any of the individual nasal symptoms.

5. CONCLUSION

Weight control should be considered as a potential strategy to improve the health status of patients with AR. This strategy could be applied together with the treatment of AR which includes the combination of allergen avoidance, pharmacotherapy and immunotherapy. Healthy weight may play an important role in preventing individuals with AR from experiencing more severe AR symptoms .The possibility that AR may lead to obesity should also be considered. For example, poor sleep associated with AR could lead to reduced energy, increased stress and stress-related eating,

and/or less inclination to exercise, resulting in excessive weight gain. Incorporating weight control in the management of AR is useful not only for reducing the severity of AR symptoms, but also for improving general health, including reducing the risk of obesity-related diseases, such as cardiovascular disease, diabetes, hypertension and stroke. Within the limitations of the current study, the research provides insight into the characteristics of patients with AR and the association between BMI and the severity of AR. These will assist in understanding and improving the management of AR. It is early to assess resistin as a biomarker or pathogenic factor in allergic rhinitis disease; although the associations of resistin with increased IgE levels and the apparent correlation with allergic disease severity make it an interesting subject for further investigation. The findings of this study also have implications for future research.

The main title (on the first page) should be centered, and in Times New Roman 18-point, boldface type. Capitalize the first letter of nouns, pronouns, verbs, adjectives, and adverbs; do not capitalize articles, coordinate conjunctions, or prepositions (unless the title begins with such a word). Please initially capitalize only the first word in (for example, "Format for Preparation of Paper for Publication in the AJCIS" — as in these guidelines).

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