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Long title: Does Serum Leptin Levels Differ between Patients with Rhinitis of Allergic vs Non-allergic Aetiology

Running Title: Leptin Levels in Allergic vs Nonallergic Rhinitis

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Abstract

BACKGROUND: Leptin may play a critical role in airway inflammation. However, it has rarely been evaluated in rhinitis with different aetiology. This study aimed to compare the serum leptin levels between allergic rhinitis (AR) and non-allergic rhinitis (NAR).

METHODS: Patients with chronic rhinitis were classified due to skin prick (ALK-Abello/Madrid) and/or serum specific immunoglobulin E tests (UniCAP 100-Pharmacia), against to aeroallergens if concordant with symptoms.

RESULTS: A total of 398 patients with a mean age of 29.03yr were recruited and grouped as AR and NAR. Mean serum leptin levels were similar in patients with NAR and AR, as well as in patients with and without asthma, but were significantly higher in females than males in both groups. Also, leptin levels were significantly higher in obese than non-obese patients in AR. In correlation analysis, leptin levels were found to be correlated with female gender, older age and high BMI in the whole group. Despite the higher TNSS in patients with AR compared to NAR, there was no association of leptin levels with TNSS, severity and seasonality of symptoms, and allergen sensitization. In logistic regression analysis; younger age and high serum leptin levels were found to be independent predictors for the diagnosis of AR.

CONCLUSIONS: We conclude that female patients with high BMI are more prone to AR probably due to immunological effects of adipose tissue, in addition to hormonal factors. This study showed that leptin measurement has limited value as a sole diagnostic tool to differentiate AR and NAR.

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KEYWORDS: asthma, allergic rhinitis, leptin, non-allergic rhinitis, obesity

INTRODUCTION

Inflammation of the nasal lining membranes, characterized by nasal symptoms, such as itching, rhinorrhea and / or nasal congestion, is defined as rhinitis. Rhinitis is classified as allergic rhinitis (AR) or non-allergic rhinitis (NAR), based on skin prick or serum specific immunoglobulin E (IgE) tests if concordant with symptoms. Although epidemiological information on NAR is limited, studies from the United States and Europe estimated that 7-19% of the adult population suffered from NAR.[1] Recently, there is a growing consensus that NAR shares a common pathway with AR in the underlying nasal mucosal inflammatory syndrome, which can lead to increased nasal congestion and consequently a wide variety of problems.[2]

Leptin is a 16-kDa protein hormone, structurally produced by white adipose tissue, a member of the interleukin (IL)-6 cytokine family. It is an anorexic peptide that has a role in hypothalamic modulation of food intake, body weight, and fat stores.[3] In addition, it has a modulator effect on the immune responses such as enhancing the production of Th1 cells to promote inflammation.[4] Furthermore, its proinflammatory effect was associated with some patterns in asthma, in relation to obesity.[5] However, its role in rhinitis is unclear. There is a close link between AR and allergic asthma such as that almost 80% of patients with asthma have rhinitis, and 30% of rhinitic patients have asthma.[6] Since the airway's lining from nose to lungs is similar in structure, it may be assumed that what affects the nose can also affect the lungs.[7] In this line if leptin has an immune-modulator effect in asthma, it may also play a role in rhinitis.[8] In this regard, leptin levels were reported to be related with AR severity.[9] Furthermore, allergen specific immunotherapy was shown to decrease leptin levels, in addition to enhancing expression of Th1 and Treg cytokines in patient with AR.[10]

As far as we know, there are no published reports in Medline about leptin levels among patients with AR and NAR. The rationale of this study was to examine the differentiative role of leptin between AR and NAR, since leptin is found to be related with inflammation in AR, as well as in asthma. Our hypothesis was that leptin was a pro-inflammatory marker of AR. The objective

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of this study was to evaluate the effect of serum leptin levels among allergic and non-allergic inflammation in rhinitis.

METHODS

This cross-sectional and prospective study was performed between 2004 – 2006, at the outpatient clinic of Allergy and Immunology Department of Kirikkale University. Ethics approval was received from the local clinical ethics committee of the Kirikkale University (09.03.2004, 2004/03), and the verbal consent of each patient participating in the study was obtained. This study was performed according to the Declaration of Helsinki II.

Study Groups

A total of 398 patients as AR (n: 300) and NAR (n: 98) were enrolled. To be eligible for participation, patients had to meet the following inclusion criteria: age between 16 and ≤65 years; persistent/intermittent rhinitis with or without asthma. Patients with pregnancy or breastfeeding, under 16 and over 65 age, who have previous systemic disease (such as diabetes) or metabolic disease other than obesity, malignancy, having collagen vascular disease, drug use that may affect leptin levels (systemic corticosteroid, insulin preparations, anti-obesity drugs, isoproterenol, propranolol) were all excluded from the study.

Diagnosis of rhinitis and asthma

Rhinitis was diagnosed if the patient had at least two symptoms of nasal itching, obstruction, rhinorrhea and sneezing at least for one hour and two consecutive days. Persistency was accepted if the rhinitis symptoms continue at least five days of the week. Severity of nasal symptoms were evaluated on a 4-point scale from 0 to 3 (0: none, 1: mild, 2: moderate, 3: severe) with total nasal symptom score (TNSS) that had a range from 0 to 12.

Asthma was diagnosed according to asthma guideline with variable airway symptoms and reversible airway obstruction in pulmonary function test.[11] Patients with asthma were enrolled only if they were under regular low dose inhaled corticosteroid treatment (budesonid or equivalent < 400 mcg / day) and had well-controlled asthma due to Asthma Control Test scores (ACT ≥ 20).

Study procedure and data collection

At the screening visit, patents were enrolled due to inclusion and exclusion criteria. If the patient was eligible, inclusion visit was performed for the following data collection. Age, gender information, and duration of rhinitis were collected. Smoking status of the patients was noted as non-smokers, ex-smokers, smokers (smoking currently and regularly as at least five cigarettes per day). Height and weight measurements were converted to body mass index (BMI;

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kg/m²). BMI ≥ 25 kg/m² were accepted as overweight and obese, and those with BMI < 25kg/m² were evaluated in two groups as normal and underweight.

Patients with a positive skin prick test (SPT; ALK-Abello/Madrid, positive: ≥3 mm in diameter) and/or specific IgE (UniCAP 100-Pharmacia, positive: ≥ 0,35 kU/L) against to aeroallergens (house dust mites, tree/grass/weed/cereal pollen mix, blattella, cat, dog, mold mix) defined as AR if their symptoms were relevant with the allergy tests. NAR was diagnosed if there was no known triggering allergen, with negativity in SPT and specific IgE. Blood samples of all groups were taken after fasting period of 12 hours in the morning and between 06:00 and 09:00. Serum samples were stored at -70 degrees.

Absorbents of serum samples were taken (μQuant Bio-Tec Instruments, INC; USA). Serum leptin levels (ng/mL) were analyzed with a solid-phase-enzyme-amplified-sensitivity-immunoassay (DIA source Immunoassays S.A. Louvain-la-Neuve, Belgium).

Statistical analysis

All data (categorical and numerical) of patients with AR and NAR were evaluated using the IBM SPSS Statistic 20 licensed program. Patients with asthma (A) in the AR and NAR groups were further analyzed as subgroups of "A + AR group" and "A + NAR group". Normality test was performed for numerical data. The averages of the groups were done with independent-samples t-test and non-normally distributed values were analyzed with Mann Whitney U test. Chi Square test was applied for categorical variables. Pearson correlation analysis was also performed between the groups. ANCOVA analysis (including gender, age, BMI, asthma and rhinitis duration) was used in a model that provided all assumptions to evaluate the leptin level in group and subgroup analysis. Multinominal logistic regression analyses were performed to identify the associations of allergic rhinitis with leptin levels, in an adjusted model of covariates including age, gender, asthma and BMI. A p value of < 0.05 was considered statistically significant.

RESULTS

In this study, 509 patients were screened, and 111 patients were excluded according to the exclusion criteria. There were 300 patients in the AR group (45 with asthma; 15%), and 98 in the NAR group (17 with asthma; 17.3%) (Table 1). Almost 2/3 of the both groups were female with a similar ratio in AR and NAR (60% and 70%, p=0.07). Mean age of NAR group was higher than AR. Mean BMI, smoking status and having asthma ratios were similar between AR and NAR groups. The duration of rhinitis was similar in both groups. The majority of

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patients in the AR group had intermittent rhinitis, whereas most of the NAR group had persistent rhinitis. Patients in the AR group had a higher TNSS compared to the NAR group ($p<0.01$), as well as they had more moderate-severe symptoms than NAR group.

Mean serum leptin levels were similar between AR and NAR groups, as well as between genders (Table 2). However, they were significantly higher in females than males in AR, and also in NAR. Mean serum leptin levels were also similar in patients with and without asthma, as well as between AR and NAR subgroups. The only difference about BMI was that mean serum leptin levels were significantly higher in obese than non-obese patients in only AR group.

In correlation analysis, leptin levels were found to be correlated with female gender, older age and high BMI ($r=0.325$, $r=0.156$, $r=0.188$ respectively, all $p<0.01$) in the whole group (Figure 1). Despite the higher TNSS in patients with AR compared to NAR, there was no association of leptin levels with TNSS, severity and seasonality of symptoms, and allergen sensitization.

Patients with AR were found to be sensitive to pollens (63.1%), house dust mite (18.6%), molds (5.5%), latex (0.8%), cat/dog (2.8%), and blatella (5.5%). Although the majority of AR patients were sensitized to outdoor allergens mostly as pollens, serum leptin values were insignificantly higher in those who were sensitized to indoor allergens as house dust mites, molds, and cat/dog.

In logistic regression analysis; younger age and high serum leptin levels were found to be independent predictors for the diagnosis of AR (Table 3).

DISCUSSION

In this study, the effect of leptin on rhinitis clinic and atopic status were investigated. The results indicated that serum leptin levels were associated with female gender, older age and high BMI in patients with rhinitis, in contrast to no association with asthma. Even though leptin levels and age were found to be risk factors for the development of AR, it was hard to explain the airway diseases risk only with leptin since several environmental factors contribute to the development of atopic diseases.

Recent studies investigating the role of leptin have indicated that leptin had effects on ventilatory function, and upper airway obstruction in obese subjects, with a pro-inflammatory role related to T cell regulation.[12,12] Leptin replacement treatment resulted to an increase in airway inflammation in addition to an elevation in eosinophils and serum IgE levels in mice after ovalbumin challenge.[13] As a result, leptin seemed to play a role in atopy by activation of IgE signaling cascades and eosinophils. However, in this study leptin levels were similar

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between allergic and non-allergic patients with rhinitis which might be explained by the role of multiple factors in the development of atopy. Furthermore, atopy development generally starts in childhood with various gene and environmental interaction. This variability is also true for factors influencing leptin secretion, such as that gender, age, adiposity, physical exercise, feeding, and caloric restriction. So, the absence of leptin difference between AR and NAR supports the above multiple interaction that it cannot be a primary factor on atopy, but it may still have indirect effects. Moreover, random selection period of patients instead of in high allergen time might have influences. For example, Unal et al. found that serum leptin levels were significantly higher in only symptomatic period in patients with AR.[14] Even though AR patients had more moderate-severe symptoms than NAR, the majority of patients in the AR group had intermittent rhinitis, and might have less symptoms during serum sample collection. In this study, there was a female gender influence on leptin levels, independent of having atopy. This result supported the previous results reported that leptin levels were higher in females than males with the similar BMI, due to the fact that women had a greater percentage of body fat as subcutaneously, that secreted leptin more intensively than visceral tissue.[15]

Leptin was previously shown to be associated with asthma, by inducing obesity, and its pro-inflammatory effect towards Th_2 polarization, and also eosinophil recruitment in previous studies.[12] However, in this study serum leptin levels were similar between patients with and without asthma both in AR in NAR. These results were in contrast to previous reports insight that hyperleptinemia contributes to enhanced pro-allergic and airway responses.[16] We suggested that the similar BMI values of asthmatic and non-asthmatic groups might be the explanation of no relation between asthma and leptin levels in addition to enrolling only well controlled asthmatics. Although previous studies had shown that increase in BMI and consequently obesity were associated with asthma prevalence, the mechanism was not yet fully understood.[17] As a result, the absence of a clear relation of leptin with asthma in patients with rhinitis and types was compatible with the one airway disease, since rhinitis and asthma share a common pathway.

However, there were some differences in subgroups such as high serum leptin levels in obese AR. This finding might be due to the difference of underlying nasal mucosal inflammation between AR and NAR. This result was also compatible with the previous results reported that obesity was linked to allergy symptoms or higher serum IgE levels.[18]

In this study, serum leptin levels were significantly correlated with older age, high BMI, and female gender, in both AR and NAR patients. Likewise, it had been suggested that the effect of adipose tissue on the immune system was more obvious in obese patients for the

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development of chronic inflammatory changes and allergic diseases.[19] This relation was also supported by the study resulting to 3 times higher frequency of specific Ig E in the obese women than non-obese ones.[20] One hypothesis is that adiposity results to up-regulate a Th2 response by elevating leptin levels and facilitating estrogen binding to upregulate receptors, thereby reducing estrogen availability which acts as a modulator of Th2 cytokine secretion such as IL-4 and IL-8 from CD4 T helper cells.[20] Furthermore, in multivariate analysis of this study, younger age and high serum leptin levels were found to be risk factors for the development of AR. In a study supporting this finding reported that high BMI was shown to be an important predictor for atopy and allergic symptoms in teenager girls.[21] We suggest that the prevalence of obesity and asthma increases by aging with a higher vulnerability in younger age, since sexual maturity may have played a role in the BMI–allergy association in teenage girls. As previously known, the higher prevalence of asthma and atopy passes from boys to girls following puberty.

On the other hand, we couldn't show a relation of leptin with NAR. We think that this relation needs further research parameters such as "general obesity" defined by BMI, and central obesity, defined by waist circumference. Han et al. reported that general and central obesity were separately associated with increased risk of NAR in adult males.[22] They explained this difference with that distinct types of adiposity had different obesity complications. Visceral adipose tissue was related to a non-allergic pro-inflammatory phenotype (Th_1 and TH_{17} cells) especially in males, whereas female obesity might be prone to AR which could be due to hormonal effects on immune responses. We conclude that female patients with high BMI seemed to be more prone to AR probably due to immunological and hormonal effects of adipose tissue.

This study had some limitations. Leptin levels in females may change throughout the menstrual cycle.[10] Serum reproductive hormone concentrations, as well as leptin levels were not measured in menstrual cycle day, therefore the role of female sex hormones couldn't be excluded in such a study group which consisted of mostly female subjects. Also, the absence of a control group was another limitation of the study.

In summary, this study has shown that higher serum leptin concentrations are associated with female gender, obesity and AR. In addition, this study has limited data to confirm the relation of leptin and asthma. We conclude that female patients with high BMI are more prone to AR probably due to immunological effects of adipose tissue, in addition to hormonal. Finally, the effect of leptin on AR and NAR are still unclear, and leptin measurement has limited value as the sole diagnostic tool when differentiating AR and NAR. Future studies are needed to confirm

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and expand of these observations to improve our understanding of the pathogenesis of AR and NAR.

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Table 1. Demographic and clinical characteristics of study groups

Variables	**AR** (n:300)	**NAR** (n:98)	**P value**
Gender, n (%);			0.06
Female Male	180 (59.5) 120 (40.5)	69 (71) 29 (29)	
Age (year)*	27.7 ± 10.4	32.9 ± 13.4	0.001
BMI (kg/m^2)*	23.78 ± 4.04	24.1 ± 3.7	0.47
Smoking status n(%);			0.57
Smoker, Exsmoker, Nonsmoker,	25 (8.3) 18 (6) 257 (85.7)	5 (5.1) 6(6.1) 87 (88.8)	
Asthma, n (%)	45 (15)	17 (17.3)	0.57
Rhinitis Duration (year)*	5.92 ± 0.29	5.9± 0.64	0.97
Rhinitis Persistency;			< 0.001
Intermittent Persistent Intermittent + Persistent	209 (69.7) 77 (25.7) 14 (4.6)	10 (10.2) 82 (83.6) 6 (6.8)	
TNSS*	7.1 ± 3.03	5.8 ± 2.56	< 0.001
Severity of Rhinitis n (%);			< 0.001
Mild Moderate - Severe	86 (28.7) 214 (71.3)	55 (56.1) 43 (43.9)	

*Mean ± standard deviation, AR: Allergic rhinitis, BMI: Body mass index, n: individual number, NAR: Non-allergic rhinitis, TNSS: Total nasal symptom score.

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Table 2. Analysis of serum leptin levels between study groups.

	AR (n: 300)	**NAR** (n: 98)	**P value**
Leptin level (ng/ml)	4.36 ± 0.25	4.04 ± 0.45	0.54
Female (n: 180-69)	5.53 ± 0.38	5.28 ± 0.63	0.73
Male (n: 120-29)	2.35 ± 0.23	2.06 ± 0.48	0.59
	AR + F (n: 180)	**AR + M** (n: 120)	
Leptin level (ng/ml)	5.53 ± 0.33	2.26 ± 0.41	<0.001
	NAR + F (n: 69)	**NAR+ M** (n: 29)	
Leptin level (ng/ml)	5.56 ± 0.50	1.82 ± 0.78	<0.001
	Non-asthmatic (n: 336)	**Asthmatic** (n: 62)	
Leptin level (ng/ml)	4.15± 0.56	4.3 ± 0.23	0.80
	AR + Asthma (n: 46)	**NAR + Asthma** (n: 17)	
Leptin level (ng/ml)	3.25 ± 0.71	3.47 ± 0.89	0.88
	AR (n: 255)	**AR + Asthma** (n: 45)	
Leptin level (ng/ml)	4.27 ± 0.27	3.94 ± 0.66	0.64
	NAR (n:81)	**NAR + Asthma** (n: 17)	
Leptin level (ng/ml)	4.39 ± 0.47	4.75 ± 1.05	0.75
	AR + BMI < 25 kg/m^2 (n: 216)	**NAR + BMI < 25 kg/m^2** (n: 81)	
Leptin level (ng/ml)	3.93 ± 0.28	3.84 ± 0.47	0.87
	AR + BMI ≥ 25 kg/m^2 (n: 84)	**NAR + BMI ≥ 25 kg/m^2** (n: 17)	
Leptin level (ng/ml)	5.52 ± 0.56	4.63 ± 1.29	0.53
	AR+ BMI < 25 kg/m^2 (n: 216)	**AR + BMI ≥ 25 kg/m^2** (n: 84)	
Leptin level (ng/ml)	3.78± 0.31	5.35± 0.54	0.01
	NAR + BMI < 25 kg/m^2 (n: 81)	**NAR + BMI ≥ 25 kg/m^2** (n:17)	
Leptin level (ng/ml)	4.44 ± 0.47	4.52 ± 1.11	0.95

* Chi-square test, ±: standard deviation, n: individual number, BMI: Body mass index, AR: Allergic rhinitis, NAR: Non-allergic rhinitis

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Table 3. Multinominal logistic regression analysis of risk factors for AR.

Predictor	Estimated β	Adjusted Odds Ratio	Confidence Interval (95%)	P value
Male	-0.936	0.392	0.183 - 0.839	0.16
Age	-0.056	0.946	0.913 - 0.979	**0.02**
Serum leptin levels	0.101	1.106	1.009 - 1.213	**0.03**
Asthma	-0.296	0.744	0.326 - 1.695	0.74
Body mass index	0.043	1.043	0.953 - 1.142	0.35

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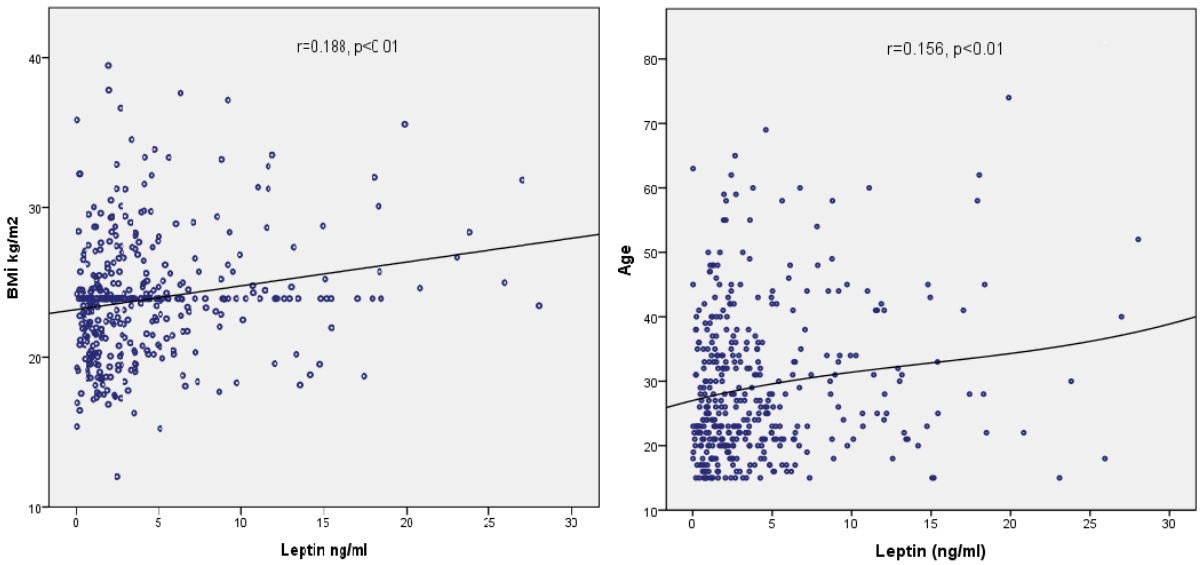


Figure 1. Correlation graph of serum leptin levels with body mass index (BMI) and age.

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