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Serum Leptin Levels in Patients with Pollen-Induced Allergic Rhinitis

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Key Words
Adipose tissue · Leptin · Allergic rhinitis · Pollen

Abstract
Background: Several studies have outlined a possible relationship between an increased body mass index (BMI) and respiratory allergic diseases, such as asthma and rhinitis. The aim of the study was to evaluate the serum leptin levels in a cohort of patients with pollen-induced allergic rhinitis, enrolled outside the pollen season, and in a group of healthy controls. ***Methods:*** The study included 75 subjects: 41 patients with moderate–severe persistent allergic rhinitis due to a pollen allergy and 34 normal subjects. All subjects were prospectively and consecutively evaluated. A skin prick test and blood sampling for assessing serum leptin levels, eosinophils, specific IgE, and nasal challenge were performed in all subjects. ***Results:*** After analyzing genders separately, female allergic patients showed significantly higher levels than normal females ($p = 0.031$), whereas the comparison between allergic and normal males was not significant ($p = 0.9651$). Leptin serum levels were significantly related with age in normal ($p = 0.0059$) and allergic ($p = 0.0042$) females. In addition, BMI and leptin levels were significantly correlated ($p = 0.01$) in all allergic patients; there were other significant relationships between leptin levels and symptom severity in females ($p = 0063$, $r = 0.68$), peripheral eosinophils in males ($p = 0.023$, $r = 0.49$), and allergen threshold dose at nasal challenge in both genders (males: $p = 0.0001$, $r = –0.85$; females: $p = 0.0001$, $r = –0.95$). ***Conclusions:*** This preliminary study provides the first evidence of significantly higher leptin serum levels in female patients with pollen-induced allergic rhinitis outside the pollen season.

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Introduction

It is well known that the prevalence of allergic disorders has increased; however, the causes of this phenomenon still remain obscure. Nevertheless, western countries have, over several hundred years, gradually changed their lifestyles and demographic constitutions. They have changed from primarily rural living and agriculture production to primarily modern urban living and industrial production. Consequently, there have been increases in mean life expectancy, hygiene, and affluence [1]. Affluence is responsible for the increased availability of food and decreased physical activity, both factors have contributed to an increase in the prevalence of excessive weight gain in up to 25% of adult men [2].

Obesity and weight gain have been associated with an increased risk of respiratory allergy [3, 4]. Most of the prospective studies have reported that obesity is a risk factor for the development of asthma, with risk or odds ratios of between 1.1 and 3.0, and that obesity precedes

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the development of asthma. Further, a significant association between body fat and asthma, mainly in women, has been found.

White adipose tissue is composed of many cell types, including adipocytes and macrophages. The identification of leptin led to the recognition that white adipose tissue represents an important endocrine organ. Indeed, adipocytes secrete a variety of protein signals, namely adipokines, including leptin and adiponectin. Leptin has an influence on the hypothalamus by inducing satiety and by increasing energy metabolism. The serum concentration of leptin is increased in obese subjects, suggesting a leptin resistance mechanism in obesity. Moreover, leptin protects T lymphocytes from apoptosis, regulates T cell proliferation and activation, recruits and activates monocytes and macrophages, and promotes angiogenesis [5, 6]. Recently, it has been reported that leptin exerts a key role in the control of the proliferation of Tregs (regulatory T lymphocytes) [7]. Thus, it has been hypothesized that an increased serum concentration of leptin would decrease the proliferation of Tregs.

In addition, exogenous leptin has been shown to modulate allergic airway responses in mice independently of obesity. Leptin infusion caused an enhancement of airway hyperresponsiveness and an increase in serum IgE after inhaled ovalbumin challenge [8]. Moreover, it has been demonstrated that human eosinophils express leptin surface receptors under in vitro and in vivo conditions, and leptin delays the apoptosis of mature eosinophils in vitro [9]. The antiapoptotic effects of leptin are concentration dependent, and blocked by an antileptin receptor monoclonal antibody. The efficacy of leptin to block eosinophil apoptosis is similar to that of GM-CSF (granulocyte monocyte colony stimulating factor). Leptin delays the cleavage of Bax, as well as the mitochondrial release of cytochrome c, a second mitochondria-derived activator of caspase, suggesting that it blocks proapoptotic pathways proximal to mitochondria in eosinophils. Leptin is therefore a survival cytokine for human eosinophils; this finding suggests potential pathologic relevance in allergic and parasitic diseases.

Leptin could also stimulate the chemokinesis of eosinophils, and induce the release of inflammatory cytokines IL-1β and IL-6, and chemokines IL-8, growth-related oncogene-α and MCP-1 [10]. In view of these findings and the elevated production of leptin in patients with allergic diseases such as atopic asthma and atopic dermatitis, leptin could play crucial immunopathophysiological roles in allergic inflammation by activation of eosinophils via differential intracellular signaling cascades [10]. In fact, serum leptin levels were found to be significantly higher in patients with allergic rhinitis in the symptomatic period [11]. Consequently, it may be hypothesized that leptin may have a role in the inflammatory process of allergic rhinitis.

Therefore, the aim of this study was to evaluate a group of patients with pollen allergy, observed outside the pollen season, and investigate the leptin serum concentration in this population.

Material and Methods

Study Design

The study included 75 subjects: 41 patients with moderate–severe persistent allergic rhinitis due to a pollen allergy and 34 normal subjects. All subjects were prospectively and consecutively evaluated. The skin prick test and blood sampling for assessing serum leptin levels were performed in all subjects, such as allergic patients and healthy subjects. The study was conducted during the winter, outside the pollen season. The study was approved by the local Ethics Committee, and performed with the written informed consent of all participants. Allergic rhinitis was diagnosed according to validated criteria [12]. Briefly, the diagnosis of allergic rhinitis was made on the basis of a positive history of nasal symptoms (i.e. nasal itching, sneezing, watery rhinorrhea, and nasal obstruction) during the pollen season for at least 2 years, and positive skin prick test for pollen allergens.

Subjects

The median age of allergic patients, 19 females (44%) and 22 males (54%), was 39 years (range 14–75). The median body mass index (BMI) was 22.3 (range 18.9–35) in allergic patients. The median age of the healthy subjects, 18 females (53%) and 16 males (47%), was 43 years (range 24–66). The median BMI was 22.8 (range 18.4–33) in normal subjects. Therefore, the 2 groups were homogeneous for these demographic parameters. Clinical and immunological characteristics are reported in table 1.

Normal subjects were healthy and did not suffer from any endocrine-metabolic or inflammatory/autoimmune disorders. Allergic patients were monosensitized to pollens alone, and did not suffer from other chronic inflammatory/autoimmune or endocrine-metabolic disorders, and were symptom free (and consequently not using any drug treatment) as the study was conducted outside the pollen season.

In order to minimize possible confounding factors, such as diet and circadian rhythms, all subjects were drawn in the morning while fasting. Moreover, in fertile females, blood was drawn during the follicular phase.

Skin Prick Test

This assay was performed according to the guidelines of the European Academy of Allergy and Clinical Immunology [13]. The panel of allergens employed consisted of: house dust mites (*Dermatophagoides farinae* and *pteronyssinus*), cat, dog, grass mix, Compositae mix, *Parietaria officinalis*, birch, hazel, olive tree, *Alternaria tenuis*, *Cladosporium*, *Aspergilli* mix (Stallergenes).

Serum Leptin Assay

The Human Leptin Immunoassay (R&D Systems) employs the quantitative sandwich enzyme immunoassay technique, and was performed according to the manufacturer's instructions with the results expressed in ng/ml. Serum samples reported for males were 4.94 (range 2.20–11.149 ng/ml) and females 10.3 (range 3.87–77.27 ng/ml).

Symptom Severity

Allergic nasal symptoms were scored by the patients referring to the immediately previous pollen season. The questionnaire included a visual analog scale (VAS) of nasal symptoms according to validated criteria [14].

Specific IgE

Serum specific IgE was measured using the fluorenzyme immunoassay (Phadia) with a calibrator range of 0–100 kU/l.

Peripheral Eosinophils

Peripheral eosinophils were evaluated as an absolute number per mm^3.

Allergen-Specific Nasal Challenge

The nasal challenge was performed according to validated criteria to confirm the diagnosis and evaluate the severity of atopy [15]; thus, the allergen threshold dose was determined for each patient and expressed as biologic units (BU).

Statistical Analysis and Data Definitions

Descriptive statistics were performed first, and quantitative parameters were reported as medians with first and third quartiles (interquartile range) due to the skewed distribution. The nonparametric Wilcoxon test was performed to evaluate the leptin differences between males and females for allergic/nonallergic subjects. The correlation between quantitative variables was evaluated by means of Pearson's correlation coefficient (r). All tests were 2 sided, and a p value less than 0.05 was considered statistically significant. The package 'S-Plus' (MathSoft) was used for all the analyses.

Results

Demographic, immunological, and clinical characteristics of allergic patients are reported in table 1.

Differences in serum leptin levels between allergic (4.62 ng/ml) and normal (4.05 ng/ml) males were not significant (p = 0.9651; fig. 1a), whereas differences between allergic (13.58 ng/ml) and normal (9.73 ng/ml) females were significant (p = 0.031, fig. 1b), i.e. allergic females had higher levels than normal females. There was a significant relationship between leptin levels and BMI, both for males (p = 0.015, r = 0.53; fig. 2a) and females (p = 0.0147, r = 0.58; fig. 2b).

The relationship between leptin levels and age was not significant for allergic males (p = 0.1677, r = 0.302; fig. 3a), whereas it was significant for allergic females (p = 0.0042, r = 0.676; fig. 3b). A similar finding has been evidenced in normal subjects, with a nonsignificant relationship for males (p = 0.6029, r = 0.136; fig. 3c) and a significant relationship for females (p = 0.0059, r = 0.669; fig. 3d).

Table 1. Demographic and clinical characteristics of patients

Patient No.	Gender	Age years	BMI	Skin prick test	Specific IgE, kU/l	ATD BU	Peripheral eosinophils n per mm^3	VAS score
1	m	39	24.2	birch	26.4	12.50	3.05	3
2	m	41	22.7	birch	94	6.00	4.10	4
3	m	18	29.1	parietaria	45	6.00	3.03	2
4	f	46	21.8	parietaria	40.4	0.50	2.20	5
5	f	58	35	grasses	83	1.00	8.03	8
6	m	26	20	parietaria	>100	12.50	3.22	5
7	f	30	20.7	parietaria	52.7	6.00	5.53	4
8	f	46	25.3	parietaria	24.7	3.00	6.44	5
9	m	59	25.9	parietaria	28.3	6.00	5.20	5
10	m	28	24.1	birch	14.6	12.50	5.05	3
11	m	53	26.4	birch	13.4	25.00	3.30	5
12	f	47	25.6	grasses	18.3	3.00	2.10	8
13	f	43	22.5	parietaria	12.5	1.50	8.10	8
14	f	32	22	birch	0.09	12.50	6.50	5
15	m	39	21.2	parietaria	8.51	13.50	2.11	5
16	m	42	25	birch	2.23	6.00	4.30	3
17	f	39	28.9	parietaria	0.8	3.00	7.45	5
18	f	75	27.3	birch	4.97	0.50	5.10	5
19	m	62	26.3	birch	11.5	24.50	4.10	8
20	f	42	21.7	grasses	7.03	12.50	5.36	5
21	m	36	22.2	birch	1.9	3.00	5.20	7
22	m	16	21.8	birch	0.36	37.50	2.38	3
23	f	32	24.5	grasses	12.9	3.00	5.40	5
24	f	42	25.3	parietaria	>100	12.50	2.12	4
25	m	33	22.6	parietaria	44	24.50	6.40	5
26	f	22	18.9	parietaria	48.5	12.50	5.22	4
27	m	15	18.9	parietaria	2.54	24.50	3.00	2
28	f	41	22.6	grasses	86.4	3.00	0.20	4
29	m	25	21.4	parietaria	61.2	6.00	6.12	4
30	m	31	26.9	birch	47.6	12.50	4.27	4
31	f	44	22.3	parietaria	84.4	3.00	7.32	8
32	f	39	20.6	parietaria	56.7	6.00	4.55	8
33	m	56	21.5	grasses	6.34	12.50	5.00	5
34	m	44	23.3	birch	51.8	12.50	8.00	3
35	m	35	20.7	parietaria	2.69	37.50	2.04	5
36	m	40	20.2	birch	77.2	50.00	2.28	5
37	f	31	21.9	birch	27.3	24.50	5.16	3
38	m	24	22.1	grasses	2.5	37.50	5.10	7
39	f	29	20.6	birch	18.9	12.50	4.40	3
40	m	14	19.9	birch	51.7	37.50	1.33	8
41	f	34	21.3	birch	1.46	12.50	8.10	4

ATD = Allergen threshold dose at nasal challenge expressed as biologic units (BU); VAS= symptom severity assessed by a visual analog scale (range = 0–10).

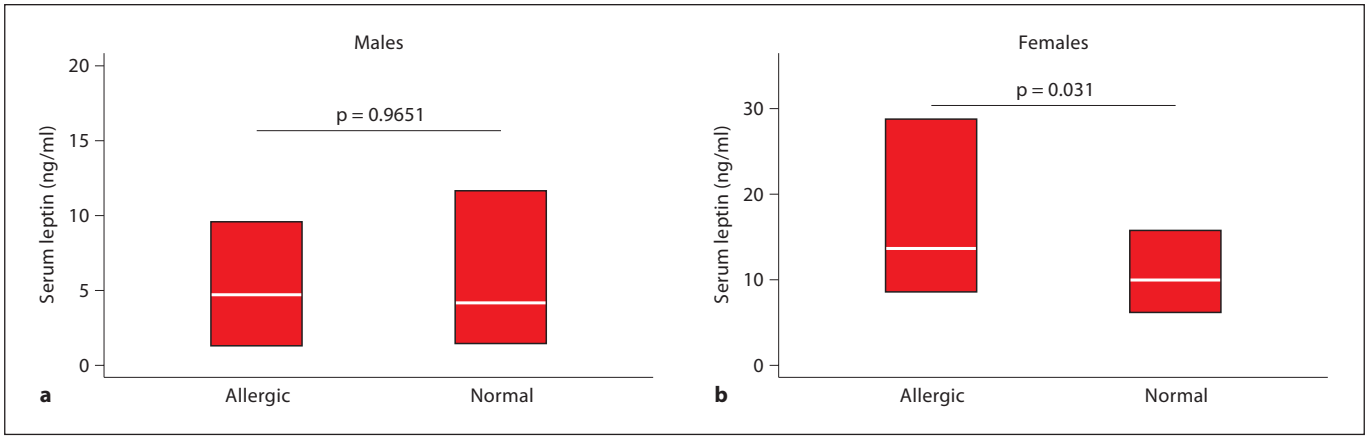


Fig. 1. Leptin distribution in allergic and healthy subjects, evaluated separately for males (**a**) and females (**b**). Data are represented as medians (white lines) and 25th and 75th percentiles (black boxes, red in online version).

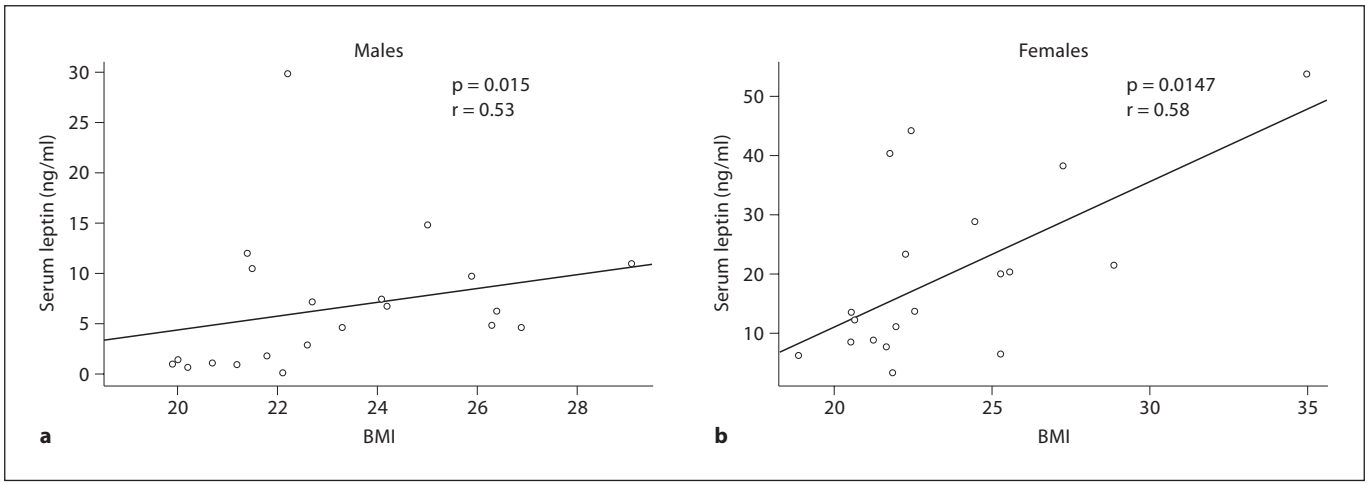


Fig. 2. Correlations, expressed with Pearson's correlation coefficient (r) and p values, between serum leptin and BMI in allergic subjects, evaluated separately for males (**a**) and females (**b**).

Moreover, there was a significant relationship between leptin levels and symptom severity assessed by the VAS in females ($p = 0063$, $r = 0.68$) as reported in figure 4a, b.

Leptin serum levels and peripheral eosinophils were significantly related in males only ($p = 0.023$ $r = 0.49$), as reported in figure 4c, d.

Finally, serum leptin levels and the allergen threshold dose for allergen-specific nasal challenge were significantly related in both genders (males: $p = 0.0001$ $r = -0.85$; females: $p = 0.0001$ $r = -0.95$) as shown in figure 4e, f.

Discussion

There is evidence that the incidence of allergic disorders, such as rhinitis and asthma, has increased in developed countries all over the world [1]. Even though several environmental factors have been hypothesized to be involved in the development of allergic diseases, none may fully explain this rapid increase in prevalence. However, some lifestyle factors, including dietary factors, alcohol consumption, physical inactivity, and obesity, have recently received close attention. Indeed, an increase in af-

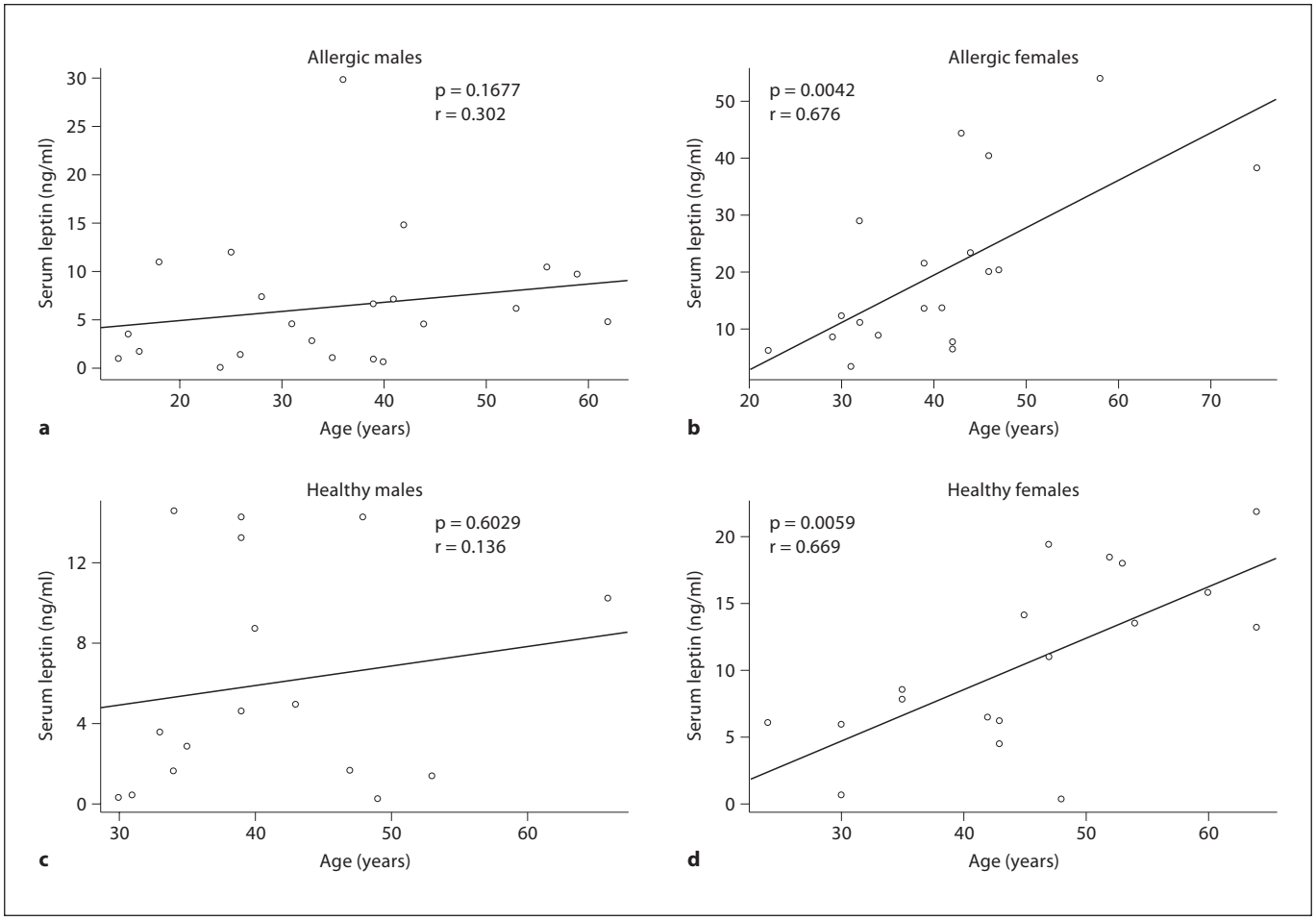


Fig. 3. Correlations, expressed with Pearson's correlation coefficient (r) and p values, between serum leptin and age in allergic and healthy subjects, evaluated separately for males (**a**, **c**) and females (**b**, **d**).

fluence, typical of western society, may have contributed to an increased availability of food and decreased physical activity, both of which may promote the prevalence of obesity. In addition, there is evidence that obesity and weight gain are linked with allergic diseases, probably through the immunological effects of adipose tissue on the development of allergies. Obesity has been associated with an increased risk of asthma both in children and adults [5, 16]. However, the real association between obesity and allergic disorders is unclear. Many cross-sectional surveys have pointed out that obesity is a risk factor for asthma, but prospective studies to define the chronological relationship between obesity and asthma are lacking. Moreover, a gender-dependent influence has been observed, and a significant association between body fat and asthma in women, but not in men, was found [3].

Moreover, only 2 studies have investigated the effects of obesity on allergic rhinitis. The first 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 [17]. The second study evidenced that the risk of allergic rhinitis increased with an increasing BMI among women, but not among men [18].

On the other hand, the association between obesity and respiratory allergy may, at least partially, depend on decreased immunological tolerance to the allergen as a consequence of immunological changes induced by adipokines, such as adiponectin and leptin, and some pro-inflammatory cytokines, including IL-6 and TNF-α, secreted by white adipose tissue. Therefore, an increase in white adipose tissue is characterized by a chronic inflam-

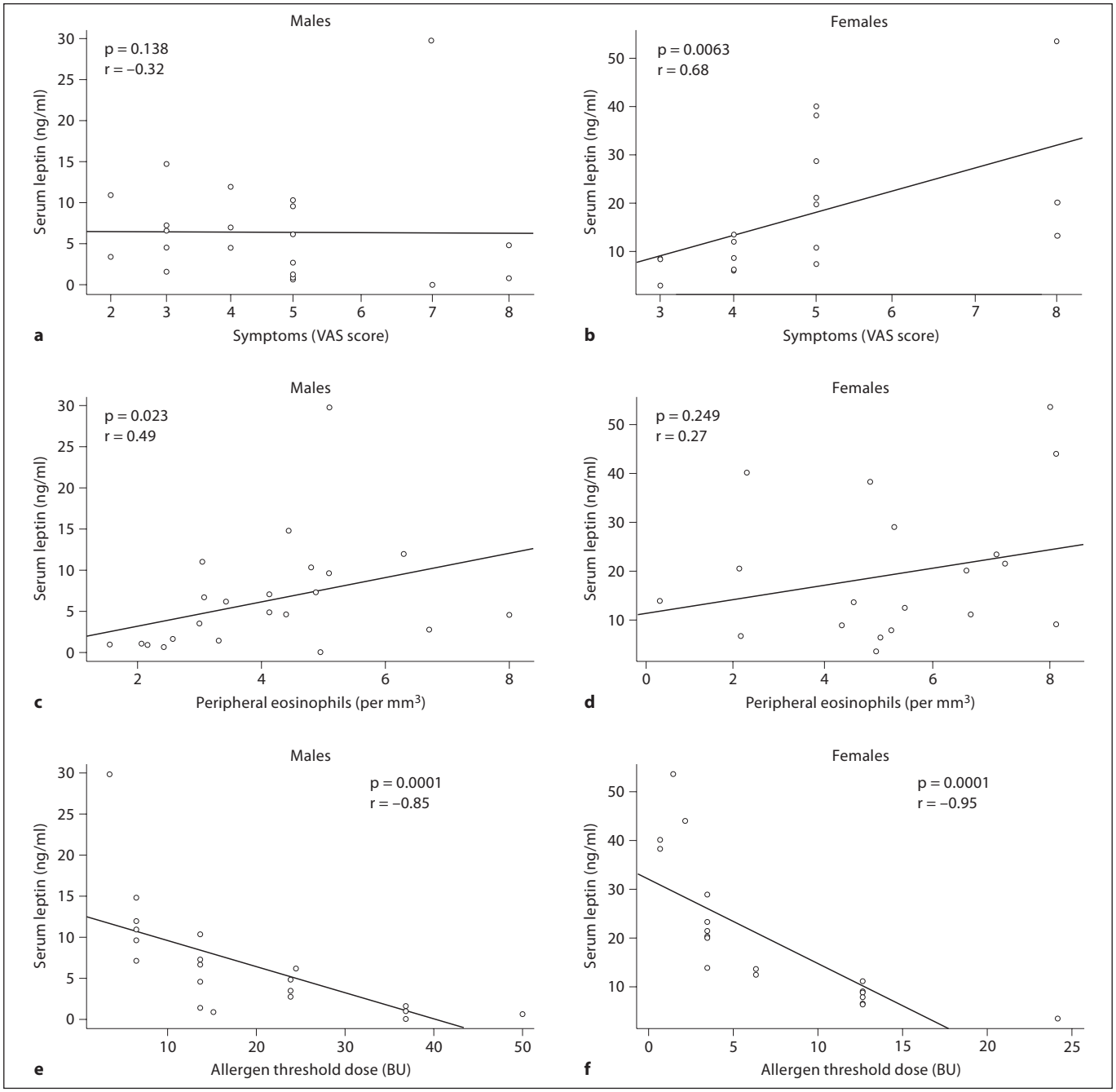


Fig. 4. Correlations between leptin serum levels and symptom severity assessed by VAS (**a**, **b**), peripheral eosinophils (**c**, **d**), and allergen threshold dose (**e**, **f**), in male and female allergic patients.

mation that skews the immune system toward a Th2 polarization; a typical condition in allergic patients. However, 2 recent studies demonstrated the absence of a significant association between body fat and airway inflammation in both sexes [3, 19].

Allergic rhinitis is characterized by Th2-polarized inflammation. Th2-derived cytokines, such as IL-4 and IL-13, are the primary pathogenic factors that induce, maintain, and amplify allergic inflammation. IL-4 and IL-13 orchestrate this inflammation by promoting IgE synthe-

sis, upregulating adhesion molecules selective for eosinophil recruitment, and causing increased mucus production and airway hyperreactivity [20]. Moreover, allergic inflammation is closely dependent on allergen exposure [21].

Leptin may be considered a proinflammatory cytokine as it is involved in eosinophil recruitment, and has been reported to be increased in patients with acute allergic rhinitis [11]. Therefore, the present study was designed to confirm the possible role of leptin in patients with allergic rhinitis. As a first step, we chose patients who were allergic to pollen only, and evaluated these subjects outside the pollen season to better define the real role of leptin in allergic patients. Indeed, these patients were symptom-free in the absence of pollen-dependent inflammation.

We felt it was important to consider leptin levels separately for each gender. The first finding indicated that there was no significant difference in serum leptin between allergic males and normal males (fig. 1a). On the other hand, we observed a significant difference between allergic females and normal females, the former showing higher leptin values (fig. 1b). In addition, BMI and leptin levels were strongly correlated both in males and females, confirming previous results [22]. This finding suggests that a resistance to leptin may exist, and depends upon an increase in adipose tissue.

Secondly, we observed a trend of increasing leptin levels with age in both allergic and normal females only. This outcome may be related to the increased adipose tissue that occurs more manifestly in females.

From analyzing these findings, it is evident that there is a relevant gender difference and there is a balance between adipokines. This finding is consistent with a recent study that evidenced that adiponectin levels are higher in allergic males [23].

Thirdly, there were significant relationships between serum leptin levels and some clinical and immunological parameters, including symptom severity, peripheral eosinophils and the degree of allergy (assessed by the allergen threshold dose for nasal challenge). These relationships outline the close correlation between leptin levels and the severity of atopy. This issue evidences the clinical relevance of the present study.

In addition, this study reflects a particular situation, i.e. allergic patients were investigated outside the pollen season. Therefore, leptin levels were not influenced by the presence of allergic inflammation, but may reflect the atopic status per se. In this regard, these data underline the concept that leptin may also exert proinflammatory effects. Indeed, leptin levels were elevated in allergic patients with acute rhinitis.

However, a very recent study showed no association between leptin plasma levels and rhinoconjunctivitis in children [24]. These conflicting results might be explained by the different characteristics of examined populations, mainly concerning the age, type of causal pollens (unfortunately, the pediatric study did not provide specific IgE evaluations), clinical diagnosis, and duration of rhinitis. In this regard, it has been recently demonstrated that the duration of allergic rhinitis may have relevant clinical and functional consequences [25, 26] that might depend on chronic stimulation of the immune response. Moreover, the gender subanalysis was not considered in this pediatric study.

In conclusion, this preliminary study provides the first evidence of significantly higher leptin serum levels in female patients with pollen-allergic rhinitis outside the pollen season, and provides support for the hypothesis that leptin exerts proinflammatory effects in this context. However, further studies, conducted in larger populations, should address and better define the roles of gender, allergen exposure, and specific immunotherapy in modulating leptin levels in allergic patients.

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