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Preliminary report

Serum adiponectin levels in patients with seasonal allergic rhinitis

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ABSTRACT

Background: A few studies have outlined a possible relationship between an increased body mass index and allergic rhinitis. A single study reported that males with seasonal allergic rhinitis (SAR), evaluated outside the pollen season, had increased serum adiponectin levels.
Objective: The aim of this preliminary study was to evaluate the serum adiponectin levels in a cohort of SAR normo-weight patients evaluated during the pollen season, comparing them with SAR patients evaluated out of pollen season and a group of healthy controls.
Methods: The study included 137 subjects; 62 SAR patients evaluated in their pollen season, while symptomatic, 41 SAR patients studied out their pollen season, while they were without symptoms, and 34 normal subjects. All subjects were consecutively evaluated. All of them were normo-weight.
A skin prick test and blood sampling for assessing serum adiponectin levels were performed in all subjects.
Results: After analysing genders separately, symptomatic male patients had significantly higher levels than both symptomless and normal males ($p = 0.0041$ and 0.0001 respectively), symptomatic female patients showed significantly higher levels than both symptomless and normal females ($p = 0.0001$ and 0.0071 respectively).
Conclusion: This study provides the preliminary evidence that adiponectin serum levels might depend on allergen exposure in SAR normo-weight patients.

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1. Introduction

The incidence of obesity and associated co-morbidities is dramatically increasing worldwide in both children and adults [1]. Obesity is characterized by a low grade systemic inflammation. In fact, inflammatory markers, such as C-reactive protein (CPR) and interleukin (IL)-6, are increased in obese subjects [1]. The presence of systemic inflammation has been linked to the increased risk of development of cardiovascular disease and type 2 diabetes in obese individuals. Some studies have also hypothesized a possible relationship between an increased body mass index (BMI) and respiratory allergic diseases such as asthma and rhinitis, with a stronger association in women [2–5]. Adipose tissue is currently viewed as an active secretory organ, sending out and responding to signals that modulate appetite, energy expenditure, insulin sensitivity, endocrine and reproductive systems, bone metabolism, inflammation and immunity [1]. Adipose tissue is composed of different cell types including adipocytes and macrophages. Although pre-adipocytes can differentiate into macrophages, it has been reported that macrophages present in adipose tissue derived from circulating monocytes that infiltrate the white adipose tissue [1,6].

Adipose tissue secretes diverse proteins, including adiponectin, leptin, resistin, adipsin, and visfatin, which can be properly classified as adipokines. Adiponectin is the most prevalent adipokine, circulating at the highest level at a concentration one thousand times greater than leptin, and exerts a role in the regulation of insulin sensitivity [7]. Although adipocytes are the most relevant source of adiponectin, serum adiponectin levels do not increase with obesity as leptin levels do. On the contrary, it has been reported a tendency for reduced adiponectin levels in obese subjects and increased levels in patients with anorexia nervosa [8]. Moreover, some experimental studies report numerous activities exerted by adiponectin on the immune response. Adiponectin reduces the production and activity of TNF-α [9]. The possible anti-inflammatory activities of adiponectin extend to inhibition of IL-6 production accompanied by induction of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist, which probably inhibit the nuclear factor kB (NF-kB) [10]. In addition, adiponectin reduces the expression of some adhesion molecules, such as ICAM-1 and VCAM [1]. Regarding this study, adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice [11]. Importantly, it has been evidenced that in children of mothers with a history of atopy, concentrations of adiponectin in cord blood could play an important role in determining risk of wheezing

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disorders in early childhood [12]. Therefore, adiponectin could appear to act as an anti-inflammatory molecule in these particular conditions.

However, only a single preliminary study has investigated adiponectin serum levels in patients with seasonal allergic rhinitis (SAR) evaluated outside the pollen season [13]. There was evidence that allergic male patients had significantly higher levels than normal males, whereas the comparison between allergic and normal females was not significant. Consequently, it may be hypothesized that adiponectin might play a role in allergic rhinitis, but it remained to demonstrate its role in the inflammatory process occurring during the pollen season.

Therefore, the aim of this study was to preliminarily evaluate also a group of normo-weight patients with symptomatic SAR, such as observed during the pollen season, and to investigate the adiponectin serum concentration in this population comparing with patients evaluated outside the season and normal subjects.

2. Methods

2.1. Study design

The study included 137 subjects; 62 normo-weight SAR patients evaluated in season, such as symptomatic, 41 SAR patients studied out season, such as symptomless, and 34 normal subjects. All subjects were consecutively evaluated. The skin prick test and blood sampling for assessing serum adiponectin levels were performed in all subjects, such as allergic patients and healthy subjects. 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 [14]. 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 since at least 2 years and positive skin prick test for pollen allergens.

2.2. Subjects

The median age of allergic patients evaluated out season, 19 females (44%) and 22 males (54%), was 39 years (range 14–75). The median age of allergic patients evaluated in season, 38 females (61%) and 24 males (39%), was 34 years (range 15–70). The median age of healthy subjects, 18 females (53%) and 16 males (47%), was 43 years (range 24–66).

The median BMI of allergic patients evaluated out season was 22.3 (range 18.9–35). The median BMI of allergic patients evaluated in season was 22.4 (range 20.3–24.4). The median BMI of healthy subjects was 22.8 (range 18.4–33).

Therefore, the three groups were homogeneous for these demographic parameters. In season SAR patients were treated only with oral antihistamines on demand and they were withdrawn at least 1 week before blood drawing.

Normal subjects were healthy and did not suffer from any disease, mainly concerning both endocrine–metabolic and inflammatory/autoimmune disorders. Allergic patients were sensitised to pollens alone and did not suffer from other chronic inflammatory/autoimmune and endocrine–metabolic disorders. In addition, we excluded patients with overweight and obesity. Prescreening of these common associated conditions by using standard diagnostic tests was performed in all study subjects (i.e. healthy and SAR subjects).

In order to minimize possible interfering factors, such as diet and circadian rhythms, all subjects were drawn in the morning and fasting. Moreover, in fertile females the blood was taken during the follicular phase. In addition, all in season SAR patients were evaluated in May: months with the highest allergen concentrations in our geographic area.

2.3. Symptom severity

Allergic nasal symptoms were scored by the symptomatic patients using a visual analogue scale (VAS) according to validated criteria [15].

2.4. Skin prick test

This assay was performed according to the guideline of the European Academy of Allergy and Clinical Immunology [16]. 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, Milan, Italy).

2.5. Serum adiponectin assay

The human Adiponectin/Acrp30 Immunoassay (R&D Systems) designed to measure total (low, middle and high) molecular weight, employs the quantitative sandwich enzyme immunoassay technique and was performed according to the manufacturer's instructions and expressed as μg/mL. The manufacturer's technical hints define the minimum detectable dose, corresponding to the zero standard concentration, arbitrarily assigned as 0.079–0.891 ng/mL and report the mean value as 6.64 μg/mL ± 3.66 SD.

2.6. Statistical analysis and data definitions

Descriptive statistics were first performed and quantitative parameters were reported as medians and standard deviation (SD) with first and third quartiles [interquartile range] due to the skewed distribution. Qualitative data were reported as absolute frequencies and percentages. The non parametric Wilcoxon test was performed to evaluate the adiponectin differences between genders and between allergic/non allergic subjects. Correlation between quantitative variables was calculated by Pearson's correlation coefficient (r). All tests were two sided and a p-value less than 0.05 was considered statistically significant. The package “S-Plus” (MathSoft Corp.) was used for all the analyses.

3. Results

The 62 SAR patients evaluated in season were allergic to birch (26), to Parietaria (24), or to grasses [12]; the 41 SAR patients studied out season were allergic to birch [17], to Parietaria [17] or to grasses [7].

The comparison between allergic patients evaluated in season and out season, without gender distinction, shows a significant difference in median serum levels of adiponectin (allergic patients in season: median 21.27 μg/mL; SD: 13.51 μg/mL. Out season: median 11.57 μg/mL; SD: 7.84 μg/mL; p-value = 0.0001); differences between allergic patients studied in season and healthy subjects (median 9.99 μg/mL; SD: 10.25 μg/mL), without gender distinction, were significant ($p = 0.0001$); whereas differences between allergic patients evaluated out season and healthy subjects, without gender distinction, were not significant ($p = 0.6226$).

Analysing genders separately, differences between allergic males evaluated in season (median: 19.09 μg/mL; SD: 11.05 μg/mL) and out season (median: 12.33 μg/mL; SD: 7.09 μg/mL) were significant ($p = 0.0041$); differences between patient males evaluated in season and healthy males (median: 8.33 μg/mL; SD: 13.41 μg/mL) were significant ($p = 0.0001$) and differences between patient males studied out season and healthy males were significant ($p = 0.0134$) (Fig. 1a and Table 1). Differences between allergic females evaluated in season (median: 25.51 μg/mL; SD: 14.62 μg/mL) and out season (median: 10.16 μg/mL; SD: 8.82 μg/mL) were significant ($p = 0.001$), differences between allergic females evaluated in season and healthy

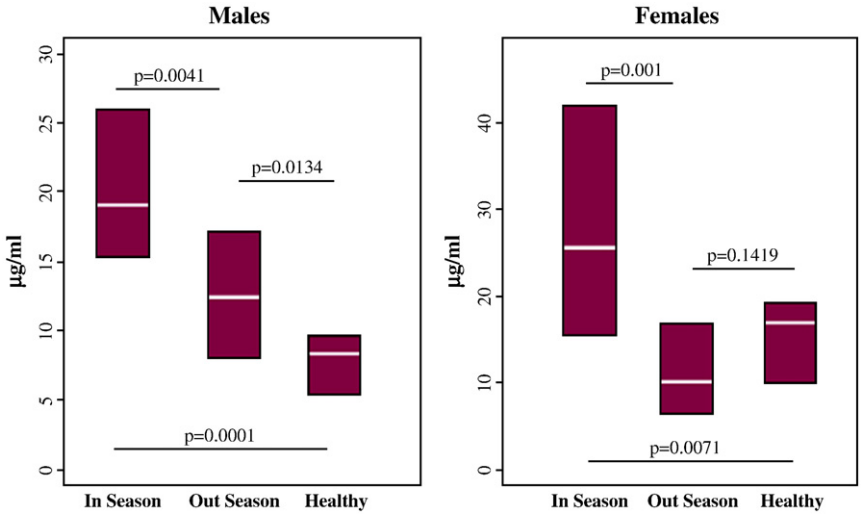

Fig. 1. Adiponectin (µg/mL) distribution in normo-weight allergic patients evaluated in pollen season, in allergic patients evaluated out pollen season, and in healthy subjects, evaluated separately for males (a) and females (b). Values are represented as medians (white line), quartiles (25th and 75th percentiles, black box), and *p* values between the groups. The Wilcoxon test was used as described in Methods.

females (median: 16.72 µg/mL; SD: 6.14) were significant ($p = 0.0071$); whereas differences between allergic females evaluated out season and healthy females were not significant ($p = 0.1419$) (Fig. 1b and Table 1).

There was no significant relationship between BMI and adiponectin serum levels ($r = 0.12$) and between type of allergy and adiponectin ($r = 0.15$) in symptomatic SAR group.

4. Discussion

There is evidence that the prevalence of allergic disorders, such as rhinitis and asthma, has increased worldwide in developed countries [17]. 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, the increase in affluence, typical of western society, may result in increased availability of foods 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 immunogical effects of adipose tissue on the development of allergies. Obesity has been associated with an increased risk of asthma both in children and adults [18,19]. 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 was observed and a significant association between body fat and asthma in women but not in men was found [2].

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 the white adipose tissue. Therefore, an increase in white adipose tissue is characterized by a chronic inflammation that skews the immune system toward a Th2 polarization; a typical condition in allergic patients. However, two recent studies demonstrated the absence of a significant association between body fat and airway inflammation in both sexes [2,20].

Therefore, the present study was designed to investigate the possible role of adiponectin in patients with seasonal allergic rhinitis, considering the effects of pollen exposure, as SAR patients were initially studied only outside the pollen season [13]. Moreover, it is to note that the selected population excluded overweight and obese subjects.

The first finding is that there is a difference between males and females, we therefore felt that it was important to consider adiponectin levels separately in each gender. In the analysis by gender, we observed a significant difference between allergic males studied outside pollen season and normal males: this difference was more relevant comparing in season patients with normal controls. In addition, a significant difference was evident comparing in season without season male patients. In addition, there was a significant difference between SAR in season females and both out season and normal females, whereas there was no significant difference between female SAR patients evaluated out season and normal females. Instead, there was no correlation between adiponectin levels and symptom severity.

Analysing these findings, it is evident that there is a relevant effect of pollen exposure. Indeed, pollen exposure induces an inflammatory response. This inflammation might be involved in complex mechanisms that implicate the adipokine network. Therefore, adiponectin levels were influenced by the presence of allergic inflammation. However, adiponectin was typically considered as an anti-inflammatory cytokine. In this regard, a very recent review underlines the concept that adiponectin may also exert pro-inflammatory effects [21]. Indeed, adiponectin levels are elevated in classic chronic inflammatory/autoimmune diseases that are unrelated to increased adipose tissue, such as rheumatoid arthritis, systemic lupus

Table 1
Serum adiponectin levels expressed in µg/mL in males and females in the studied groups.

	Males			Females		
	Out season	In season	Healthy	Out season	In season	Healthy
25th	8.00	15.42	5.49	7.19	15.69	10.03
Median	12.33	19.09	8.33	10.16	25.51	17.45
75th	17.14	26.05	9.50	16.25	42.05	19.07
Standard deviation	7.09	11.05	13.41	8.82	14.62	6.14

erythematosus, inflammatory bowel disease, type 1 diabetes, and cystic fibrosis. In these patients, adiponectin levels positively correlate with inflammatory markers. Thus, adiponectin is regulated in the opposite direction and may exert different functions in classic versus obesity-associated inflammatory disorders, and allergic diseases are chronic inflammatory disorder. Therefore, adiponectin may exert multifunctional activities depending on the immunologic milieu.

The present findings might support the idea that adiponectin levels are increased in allergic patients confirming the hypothesis that adiponectin might exert pro-inflammatory effects in this context. However, this study is lacking cytokine investigations and measurements of regulatory effects of gene expression correlated to adiponectin in human serum, therefore further functional studies should be addressed to investigate this issue and confirm this hypothetical scenario, mainly concerning the relevance of body weight. In addition, a relevant limitation of this study concerns a main question which remains open concerning the correlation of obesity and atopic diseases. In fact, this study included normo-weight symptomatic SAR patients alone to better investigate the possible *per se* role of adiponectin in allergic rhinitis. Further studies should investigate this issue.

In conclusion, this study provides the preliminary evidence that serum adiponectin might depend on allergen exposure in normo-weight SAR patients and provides support for the hypothesis that adiponectin might exert pro-inflammatory effects in this context.

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