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RESEARCH ARTICLE

Leptin and adiponectin in obese and non-obese subjects with asthma

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Abstract

Objective: To understand the role of leptin and adiponectin in obese asthmatics.

Methods: We compared serum leptin, adiponectin and sputum leptin levels in 44 non-obese and 44 obese subjects.

Results: We found higher serum leptin ($P < 0.0001$) and lower adiponectin ($P = 0.0002$) levels in obese asthmatics. Sputum leptin was correlated with body mass index (BMI; $r = 0.34$, $P = 0.03$) and serum leptin ($r = 0.43$, $P = 0.005$); however, this last correlation was not significant after adjusting for BMI ($r = 0.26$, $P = 0.11$).

Conclusion: Airway inflammation in obese asthmatics may present a different pattern involving leptin. Sputum leptin levels may partially originate from systemic circulation, with other contributing mechanisms.

Keywords: Asthma, leptin, adiponectin, obese asthmatics

Introduction

Obesity is associated with an increased risk of asthma (Boulet and Des Cormiers, 2007). Leptin, a pro-inflammatory hormone, is associated with an increased prevalence of asthma in children (Mai et al., 2004) and adults (Sood et al., 2006). Although the efficacy of inhaled corticosteroids (ICS) to help achieve asthma control seemed to be reduced in obese asthmatic patients, this was not observed with leukotriene antagonists, suggesting an increased role of leukotrienes in obese asthmatic subjects (Peters-Golden et al., 2006). In mice, leptin has been shown to increase the synthesis of leukotrienes in macrophages (Mancuso et al., 2004).

Adiponectin, an anti-inflammatory hormone, is decreased in serum of obese subjects (Fantuzzi, 2008). In mice, adiponectin infusion reduces airway responsiveness and Th2 cytokines expression (Shore et al., 2006). In humans, high levels of adiponectin have been associated with reduced odds of asthma in pre-menopausal women (Sood et al., 2008). The aim of this study was to better understand the role of leptin and adiponectin in asthma among obese subjects.

Methods

We herein report an analysis performed in subjects taking part in our research program on the links between obesity and asthma, which was registered with Clinical Trials ID: ORPA–NCT 00532363 and NCT 00532831 (Lessard et al., 2008). The protocol was reviewed and approved by the local institutional ethics committee. All patients signed an informed consent. Briefly, 44 obese (body mass index [BMI] ≥ 30 kg/m^2) and 44 non-obese subjects (BMI < 25 kg/m^2) were paired for age, sex and asthma maintenance treatment. Asthma diagnosis was confirmed by methacholine challenge and atopy evaluated with skin prick tests. Sputum induction and analysis were performed using the method modified by Pizzichini et al. (Pizzichini et al., 1996) and serum samples were obtained. Serum leptin, adiponectin and sputum leptin levels were measured with ELISA kits (R&D Systems Inc., Minneapolis, MN, USA). The minimum detection limits of leptin and adiponectin were respectively 7.8 pg/ml and 0.246 ng/ml.

Variables were expressed using mean ± SD and were compared using the Student's *t*-test. Relationships

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between variables were measured using the Spearman's correlation coefficient or linear regression adjusted with first-order partial correlations. A P value < 0.05 using a two-tailed test was considered significant. Data analysis was performed using SAS v9.1.3 and StatView v5.0.1 (SAS Institute Inc.).

Results

Subjects' characteristics are summarized in Table 1. Half of subjects used monotherapy with a short-acting β_2-agonist (SABAs), while the other half took SABAs and ICS. All patients were considered to have adequate asthma control with their respective medication, according to the treating physician. Twenty-five obese and 23 non-obese subjects provided sputum samples.

As expected, serum leptin levels were higher (57.7 ± 30.6 ng/ml vs. 19.5 ± 19.5 ng/ml, $P < 0.0001$) and serum adiponectin levels lower (12.0 ± 6.1 ng/ml vs. 17.5 ± 8.5 ng/ml, $P = 0.0002$) in obese compared with non-obese subjects. Sputum leptin levels were similar in both obese (13.7 ± 13.2 ng/ml) and non-obese subjects (11.3 ± 11.2 ng/ml). However, for the whole group of subjects, sputum leptin levels were significantly correlated with BMI ($r = 0.34$, $P = 0.03$). Sputum leptin levels were also correlated with serum leptin levels ($r = 0.43$, $P = 0.005$), but this correlation did not remain significant after adjusting for BMI ($r = 0.26$, $p = 0.11$).

Subjects taking ICS and SABAs had similar serum leptin (43.8 ± 35.5 vs. 32.8 ± 27.0 ng/ml, $P > 0.05$) and higher serum adiponectin (17.2 ± 8.1 vs. 12.3 ± 6.9 ng/ml, $P = 0.003$) levels than those using SABAs only. Sputum leptin levels were significantly higher in subjects with ICS and SABAs (14.9 ± 5.9 ng/ml) compared with those taking SABAs only (5.9 ± 7.2 ng/ml, $P = 0.02$).

Table 1. Subjects' characteristics and results for serum leptin, adiponectin and sputum leptin

	Obese subjects (BMI ≥ 30 kg/m^2)	Non-obese subjects (BMI < 25 kg/m^2)
	$n = 44$	$n = 44$
Age, years*	40 ± 14	38 ± 13
Number of women (n)	37	37
SABAs (n)	22	22
ICS and SABAs (n)	22	22
ICS (μg/d)**	827 ± 282	814 ± 247
BMI*	37 ± 6	23 ± 2
Waist circumference*	108 ± 14	78 ± 8
Ex-smokers (n)	30	26
Pack-years smoked*	8 ± 7	4 ± 3
Atopy (n)	36	39
PC_{20} methacholine (mg/ml)*	2	2
Serum leptin (ng/ml)†	57.7 ± 30.6	19.5 ± 19.5
Serum adiponectin (ng/ml)‡	12.0 ± 6.1	17.5 ± 8.5
Sputum leptin (ng/ml)	13.7 ± 13.2	11.3 ± 11.2

BMI, body mass index; ICS, inhaled corticosteroids; SABAs, short-acting β_2-agonists; PC_{20}, provocative concentration of methacholine inducing a 20% fall in FEV_1.
*Mean ± SD.
**Equivalent of CFC-beclomethasone.
†$p < 0.0001$.
‡$p = 0.0002$.

Discussion

We found a positive correlation between sputum leptin levels and BMI, in keeping with a different pattern of airway inflammation among obese subjects (Lessard et al., 2008; van Veen et al., 2008), which could possibly explain the poorer response to asthma medication in obese subjects (Boulet and Franssen, 2007). We also found a significant correlation between serum and sputum leptin levels, suggesting that leptin may originate from the systemic circulation. However, this correlation was no longer significant after adjusting for BMI, suggesting that other mechanisms than those associated with obesity may contribute to changes in its production.

Subjects on ICS have usually more severe asthma than those with SABAs only. In our study, serum adiponectin levels were increased in subjects on ICS, suggesting either an effect of ICS itself on adiponectin levels or an unknown association between adiponectin and asthma severity. In this way, adiponectin levels are increased in chronic inflammatory diseases such as rheumatoid arthritis and adiponectin (Fantuzzi, 2008). However, in asthma, adiponectin levels are lower than in non-asthmatic subjects (Sood et al., 2008). Sputum leptin levels were also higher in subjects with ICS. The local effect of ICS on sputum leptin levels or its association with asthma severity need to be further explored. Finally, contrary to Gurkan et al. (Gurkan et al., 2004), we found no difference in serum leptin levels related to ICS use. However, our subjects were adults and used ICS for a long time period.

Our study has obviously some limitations. First, 84% of the people enrolled were women and only 58 subjects provided a sputum sample, limiting the power and the generalizability of the study. Second, the validity of the ELISA kit for leptin in sputum supernatant is unknown. A previous study has shown that the presence of DTT resulted in an inhibition of 10% of leptin levels (Broekhuizen et al., 2005). Although the absolute sputum leptin levels in our analysis may be underestimated, it should not affect the correlations and comparisons between subjects. Finally, we did not succeed in measuring sputum adiponectin levels as most measures were under the detection limit. Sputum induction may therefore not be appropriate to evaluate local airway adiponectin levels.

A study on chronic pulmonary obstructive disease (COPD; Broekhuizen et al., 2005) showed that in 14 male patients with moderate COPD, leptin was detectable in induced sputum of 10 patients and that a significant relationship was found between sputum leptin and CRP and total tumor necrosis factor-α, while

plasma leptin and sputum leptin were inversely correlated. This may indicate that leptin is involved in the local inflammatory response in COPD, but our study suggest a different role of leptin in asthma compared to COPD, possibly related to the fact that systemic inflammation seems more marked in COPD than in asthma. These observations certainly suggest that further studies should be done to really assess properly this parameter and the possible role of leptin in these conditions.

In conclusion, our results suggest that airway inflammation in obese asthmatics may present a different pattern in which leptin may be implied. Increased sputum leptin levels with increased BMI may partially originate from systemic circulation but other mechanisms seem also to contribute. Combined with other evidences of the literature, these results could explain the poorer response to asthma medication in obese subjects. Finally, the relationship between adipokine levels, ICS and asthma severity need to be further explored.

Declaration of interest

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