

The influence of leptin on Th1/Th2 balance in obese children with asthma*

Influência da leptina no equilíbrio Th1/Th2 em crianças asmáticas obesas

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Abstract

Objective: In individuals with asthma, obesity induces the production of leptin and is associated with disease severity. Our objective was to evaluate the levels of serum leptin and their effect on Th1/Th2 balance in obese and non-obese children with asthma, as well as to investigate the association between serum leptin levels and clinical outcomes. **Methods:** We evaluated 50 atopic children with physician-diagnosed moderate-to-severe persistent asthma and 20 controls. The children with asthma were divided into two groups, by body mass index percentile: obese (n = 25) and non-obese (n = 25). From all subjects, we collected peripheral blood samples in order to determine the levels of leptin, IFN- γ , and IL-4. Asthma severity was assessed by an asthma symptom score, and the results were correlated with the parameters studied. **Results:** Serum leptin levels were significantly higher in the obese asthma group than in the non-obese asthma group, as well as being significantly higher in the children with asthma than in the controls, whereas IFN- γ levels were significantly higher and IL-4 levels were significantly lower in the obese asthma group than in the non-obese asthma group. In addition, the obese asthma group showed higher asthma symptom scores and significantly lower FEV₁ (% of predicted) than did the non-obese asthma group. There was a significant positive correlation between leptin and IFN- γ levels only in the obese asthma group. **Conclusions:** Although leptin is involved in the pathogenesis of asthma in obese and non-obese children, its effect is more pronounced in the former. In the presence of high leptin levels, only obese children with asthma exhibited Th1 polarization, with higher IFN- γ levels and greater asthma severity.

Keywords: Leptin; Asthma; Interferon-gamma; Interleukin-4.

Resumo

Objetivo: A obesidade induz a produção de leptina em asmáticos e está associada à gravidade da doença. Nosso objetivo foi avaliar os níveis de leptina sérica e seu efeito no equilíbrio Th1/Th2 em crianças asmáticas obesas e não obesas e investigar a associação desses níveis com desfechos clínicos. **Métodos:** O estudo envolveu 50 crianças atópicas com diagnóstico médico de asma persistente moderada a grave e 20 controles. Os asmáticos foram agrupados como obesos (n = 25) e não obesos (n = 25) de acordo com o percentil do índice de massa corpórea. Amostras de sangue periférico foram coletadas de todos os sujeitos, e os níveis de leptina, IFN- γ e IL-4 foram determinados. A gravidade da asma foi avaliada por um escore de sintomas de asma, e os resultados foram correlacionados com os parâmetros estudados. **Resultados:** Os níveis séricos de leptina foram significativamente maiores nos asmáticos obesos do que nos asmáticos não obesos, assim como nos asmáticos comparados aos controles, enquanto os níveis de IFN- γ foram significativamente maiores e os de IL-4 foram significativamente menores nos asmáticos obesos do que nos asmáticos não obesos. Os asmáticos obesos tiveram maiores escores de sintomas de asma e VEF₁ (% do previsto) significativamente menor que os asmáticos não obesos. Houve uma correlação positiva significativa entre os níveis de leptina e IFN- γ somente entre os asmáticos obesos. **Conclusões:** Embora a leptina esteja envolvida na patogênese da asma em crianças asmáticas obesas ou não, seu efeito é maior naquelas obesas. Na presença de altos níveis de leptina, somente as crianças asmáticas obesas apresentaram polarização Th1 com maiores níveis de IFN- γ e asma mais grave.

Descritores: Leptina; Asma; Interferon gama; Interleucina-4.

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Introduction

Asthma represents a chronic inflammatory disorder of the airways and is associated with airway hyperresponsiveness that leads to recurrent episodes of often reversible, widespread airflow obstruction within the lung.⁽¹⁾ It has become clear that obesity is associated with a systemic inflammatory state.⁽²⁾ The increase of adipose tissue in obese subjects produces a rise in the serum concentrations of various pro-inflammatory cytokines, chemokines, and adipokines, which can also result in airway hyperreactivity.⁽³⁾

Obesity is a risk factor for asthma.⁽⁴⁾ Adiposity might increase the severity of asthma and alter the efficacy of standard asthma medications.⁽⁵⁾ Although the mechanisms underlying the relationship between obesity and asthma have yet to be fully established, experimental evidence suggests that changes in adipose tissue-derived hormones, including the adipokine leptin, as well as other factors, are implicated.⁽⁶⁾

Leptin is one of the adipose tissue-derived energy-regulating hormones and a product of the obesity gene. Circulating leptin is positively correlated with body fat percentage and body fat mass. In addition to its primary effects on energy regulation, which it exerts by inhibiting food intake and increasing energy expenditure, leptin has been found to play a regulatory role within the immune system.⁽⁷⁾ The regulatory capacity of leptin is associated not only with adaptive immunity but also with the innate system.⁽⁶⁾

Leptin promotes the production of nitric oxide and pro-inflammatory cytokines in macrophages and monocytes.⁽⁸⁾ Leptin has recently been shown to stimulate the production of TNF- α and IL-6 by adipose tissue,⁽⁹⁾ as well as the release of reactive oxygen species by neutrophils.^(10,11)

Because leptin receptors are expressed on T lymphocytes, leptin promotes T lymphocyte survival, proliferation and cytokine production, although the effects of leptin are seen only in Th1 lymphocytes, with increased production of IFN- γ ,⁽⁸⁾ and not in Th2 lymphocytes, which also produce cytokines.⁽¹²⁾ The cytokine IFN- γ , which is predominantly derived from T cells and natural killer T cells,⁽¹³⁾ plays an important role in the innate and adaptive immune responses, particularly regarding viral infections. Because IFN- γ is primarily secreted by T cells and natural killer T cells,⁽¹⁴⁾ emerging evidence suggests that increases in the T-cell population in adipose tissue

and leptin modulation of T cells to a Th1 immune response, with increased production of IFN- γ ,^(12,14) contribute to obesity in subjects with a specific asthma phenotype.

The aim of the present study was to evaluate the levels of serum leptin and their effect on Th1/Th2 balance by measuring the hallmark Th1 cytokine (IFN- γ) and the hallmark Th2 cytokine (IL-4) in obese and non-obese children with asthma, as well as to investigate the association between serum leptin levels and clinical outcomes.

Methods

This was a case-control study involving 50 atopic children with moderate-to-severe persistent asthma and a control group of 20 non-obese children without asthma. The children in the former group were diagnosed with asthma by a pediatric pulmonologist in accordance with the Global Initiative for Asthma guidelines at least six months prior to the beginning of the study and had been followed in the Asthma and Allergy Section of the Pediatrics Department of the Zagazig University Hospital System, located in the city of Cairo, Egypt.

The exclusion criteria were use of corticosteroids one week prior to blood collection and use of asthma medications, such as bronchodilators, 24 h prior to blood collection. In addition, children with any other acute or chronic disease, including acute upper/lower respiratory tract infection and heart, brain, or endocrine disease were excluded, as were those with a history of infectious disease in the last two months or having used any medications in the last week.

The children with asthma were divided into obese and non-obese groups according to their body mass index (BMI) percentile. Obesity was defined as having a BMI, calculated as weight (kg)/height²(m²), above the 95th percentile for age and gender.⁽¹⁵⁾ All of the children diagnosed with asthma met the diagnostic criteria for bronchial asthma developed by the Global Initiative for Asthma.⁽¹⁶⁾

Sociodemographic characteristics of the children, including age and gender, were recorded. Height and weight were measured using a stadiometer and an electronic scale, respectively, under the supervision of the researchers. Asthma symptom scores were assessed and recorded for the children with asthma. Serum leptin, IL-4, IFN- γ , and IgE levels were determined. On the day of sample collection, FEV₁ (% of predicted) was also measured.

Table 1 – Demographic and clinical data of the participants, by group.^a

Variable	Groups			p
	Asthma		Control	
	Obese	Non-obese		
	(n = 25)	(n = 25)	(n = 20)	
Age, years	9.3 ± 2.5	10.4 ± 1.3	5.5 ± 1.8	> 0.05*
Male gender ^b	12 (60)	11 (55)	9 (45)	> 0.05**
Female gender ^b	8 (40)	9 (45)	11 (55)	
FEV ₁ , % of predicted	81.4 ± 13.8	89.8 ± 15.1	96.1 ± 10.2	< 0.05*
Body mass index	25.1 ± 6.8	18.6 ± 2.8	18.1 ± 3.2	< 0.0001*
Asthma symptom score	10.9 ± 2.8	8.1 ± 2.4	N/A	< 0.001*

^aValues expressed as mean ± SD, except where otherwise indicated. ^bValues expressed as n (%). *F test. **Chi-square test.

Table 2 – Laboratory data of the of the participants, by group.^a

Variable	Groups			p*
	Asthma		Control	
	Obese	Non-obese		
	(n = 25)	(n = 25)	(n = 20)	
IgE, IU/mL	220.0 ± 30.5	244.0 ± 29.9	55.0 ± 8.5	< 0.05
IL-4, pg/mL	30.0 ± 8.2	89.0 ± 20.9	10.0 ± 2.2	< 0.05
IFN-γ, pg/mL	203 ± 36	40.8 ± 11.3	20 ± 9.5	< 0.05
Leptin, ng/mL	43.8 ± 3.9	31.3 ± 2.8	12.1 ± 1.4	< 0.05

^aValues expressed as mean ± SD. *F test.

The study was approved by the research ethics committee of the university. The parents or legal guardians of the children gave written informed consent.

Symptom scores in children with asthma were assessed in accordance with a six-domain asthma symptom score.⁽¹⁷⁾ The items in the scale included dyspnea, tightness in the chest, wheezing during the day, wheezing during the night, and daily performance, scored from zero to three by severity.

Bronchodilator use was discontinued prior to lung function testing (short-acting bronchodilators were discontinued at least 8 h prior to the test). Dynamic spirometry was performed with a pneumotachograph (Masterlab Jaeger, Würzburg, Germany). The determination of FEV₁% was in accordance with the European Respiratory Society standards. The highest FEV₁ value obtained in three maneuvers was used for data analysis.

For the measurement of leptin, IL-4 and IFN-γ levels, venous blood samples (2 mL) were obtained at 9:00 a.m. after an overnight fast. Blood samples were allowed to clot at

room temperature for 60 min. The serum was separated by centrifugation at 1,200 g for 10 min and stored at -80°C. Serum samples were thawed at room temperature before the measurements.

Serum leptin levels were determined using a double-antibody sandwich ELISA method with a specific human leptin antibody (R&D Systems, Minneapolis, MN, USA). The sensitivity of the assay was 0.1 ng/mL, and the intra-assay proportional coefficient of variation was 3.6. The minimum detectable dose of leptin is typically < 7.8 pg/mL. Serum IL-4 and IFN-γ levels, as well as total IgE levels, were measured using ELISA (R&D Systems). Serum samples were stored at -70°C until the assay was performed.

Statistical analysis was performed with the Statistical Package for the Social Sciences, version 13.0 (SPSS Inc., Chicago, IL, USA). The data are expressed as mean ± SD. Comparison of parameters between the groups was performed using one-way ANOVA. Pearson's correlation analysis was used in order to evaluate the relationship between

Table 3 – Correlation between leptin levels and other parameters in obese children with asthma.

Parameter	r	p
IFN- γ	0.53	< 0.001
Asthma symptom score	0.29	< 0.05
IgE	0.03	> 0.05
IL-4	-0.032	> 0.05
FEV ₁ , % of predicted	-0.49	> 0.05

Table 4 – Correlation between IFN- γ levels and other parameters in obese children with asthma.

Parameter	r	p
Leptin	0.53	< 0.001
Asthma symptom score	0.61	< 0.001
IgE	0.27	> 0.05
IL-4	-0.18	> 0.05
FEV ₁ , % of predicted	-0.59	< 0.05

the parameters. The level of significance was set at $p < 0.05$.

Results

The mean ages of the obese children with asthma ($n = 25$), non-obese children with asthma ($n = 25$), and controls ($n = 20$) were 9.3 ± 2.5 , 10.4 ± 1.3 , and 10.7 ± 2.9 years, respectively ($p = 0.06$). Males constituted 60%, 55%, and 45% of the respective groups ($p = 0.66$; Table 1).

As expected, the mean BMI was significantly higher in the obese asthma group than in the non-obese asthma and control groups ($p < 0.001$; Table 1). The mean asthma symptom score was significantly higher in the obese asthma group than in the non-obese asthma group (10.9 ± 2.8 vs. 8.1 ± 2.4 ; $p < 0.001$; Table 1).

The mean FEV₁, % was significantly lower in the obese asthma group than in the non-obese asthma group ($81.4 \pm 13.8\%$ vs. $89.8 \pm 15.1\%$; $p < 0.005$; Table 1).

Mean leptin levels differed significantly among the obese asthma, non-obese asthma, and control groups (43.8 ± 3.9 pg/mL; 31.3 ± 2.8 pg/mL; and 12.1 ± 1.4 pg/mL, respectively; $p < 0.05$ for all; Table 2), as did mean IFN- γ levels (203 ± 36 pg/mL; 40.8 ± 11.3 pg/mL; and 20.0 ± 9.5 pg/mL, respectively; $p < 0.05$ for all) and mean serum IL-4 levels (30.0 ± 8.2 pg/mL; 89.0 ± 20.9 pg/mL; and 10.0 ± 2.2 pg/mL; $p < 0.05$ for all; Table 2).

In the obese asthma group, leptin levels showed significant positive correlations with IFN- γ levels ($r = 0.53$) and asthma symptom scores ($r = 0.29$), as well as a significant negative correlation with FEV₁, % ($r = -0.49$). However, there was no significant correlation between leptin and IL-4 levels (Table 3).

In the obese asthma group, IFN- γ levels showed a significant positive correlation with the asthma symptom scores ($r = 0.61$) and a negative correlation with FEV₁, % ($r = -0.59$). Again, no significant correlation was found between IFN- γ and IL-4 levels (Table 4). In the non-obese asthma group, leptin levels correlated significantly only with asthma symptom scores.

Discussion

In the modern world, there is a trend toward an increase in the frequency of obesity and asthma.⁽¹⁸⁾ Elucidation of the pathogenic mechanism of the association between these two entities might aid in resolving therapeutic failure in obese children with asthma.⁽¹⁸⁾ Recently, hormones and cytokines released from adipose tissue have been the focus of research regarding this association.⁽¹⁸⁾

Leptin, a hormone of adipose tissue, is associated with inflammation,⁽¹⁹⁾ and its levels have been shown to be higher in children with asthma than in those without.⁽²⁰⁾ However, studies of the relationship between leptin and asthma in children have yielded inconsistent results.^(3,20)

We observed increased leptin levels in obese and non-obese children with asthma when compared with controls, and this difference was most pronounced in obese children with asthma. This suggests that leptin plays a role as an inflammatory mediator in asthma, in support of previous reports of its inflammatory characteristics.⁽²¹⁾

In our study, FEV₁, % was lower and asthma symptom scores were higher in the obese children with asthma than in the non-obese children with asthma. This suggests that higher leptin levels in the obese children with asthma contributed to their higher symptom scores and reduced lung function in comparison with the non-obese children with asthma. Sin and Man demonstrated that high concentrations of leptin are associated with impaired lung function in obese subjects.⁽²²⁾

In the present study, leptin levels were positively correlated with asthma symptom scores in obese and non-obese children with asthma and negatively correlated with FEV₁, % only in obese children with

asthma. That indicates that, in addition to the pronounced effect of leptin in obese children with asthma, leptin also plays a role in the inflammatory response in non-obese children with asthma.

In one clinical study, Gurkan et al. demonstrated that, in children with recently diagnosed asthma (before treatment with budesonide), serum levels of leptin were higher than in BMI-matched children without asthma.⁽²³⁾ Guler et al. reported that a one-unit increase in log leptin levels represented a twofold increase in the OR for asthma after adjustment for BMI.⁽²⁴⁾

Mai et al. studied the association between serum leptin levels and asthma in overweight and non-overweight children in Sweden.⁽²⁵⁾ They found that serum leptin levels were twice as high in overweight children with asthma than in overweight children without asthma. Among non-overweight children, however, the authors found serum leptin levels to be similar between children with and without asthma. Therefore, regarding the interactive effect of leptin and obesity in asthma, the data favor the hypothesis that leptin plays an important role in the inflammatory pathogenesis of asthma, and that this role has a more pronounced effect on obese individuals with asthma that is more severe.

In addition to its endocrine and metabolic function, leptin enhances the Th1 response, suppresses Th2 pathways, and can exert direct effects on CD4+ T lymphocyte proliferation and macrophage phagocytosis. In obese children, leptin promotes IFN- γ production in naive cells and memory T cells but inhibits IL-4 synthesis in memory T cells.⁽²⁶⁾

We found that IFN- γ levels were significantly elevated and IL-4 levels were decreased only in obese children with asthma, with a significant positive correlation between IFN- γ and serum leptin levels. Thus, airway inflammation in obese children with asthma might present a different pattern with a shift to a Th1-cytokine profile dominated by the production of IFN- γ and mediated by leptin. Lord et al. and La Cava et al. demonstrated that the actions of leptin on the immune system are complex and that IFN- γ levels are significantly enhanced by leptin.^(26,27) Fernandez-Real et al. reported that, in a mixed lymphocyte reaction, leptin supported T cell differentiation toward the Th1 phenotype.⁽²⁸⁾

In the present study, IFN- γ levels were positively correlated with the asthma symptom scores and negatively correlated with FEV₁% only in obese children. Our data suggest that, in the presence of high leptin levels, there is an increase in IFN- γ production by Th1-polarized cells,^(22,28) with aggravation of airway inflammation and clinical outcomes that are more severe. Our data are corroborated by Rastogi et al., who demonstrated that obese children with asthma had lower FEV₁/FVC ratios than did non-obese children with asthma and children without asthma, and that the FEV₁/FVC ratio was negatively correlated with serum IFN- γ levels.⁽²⁹⁾ In addition, a greater proportion of IFN- γ -secreting CD4+ T cells was observed in blood samples of obese children than in those of lean children, and that difference correlated with serum leptin levels. Our findings corroborate those of Yuksel et al., who concluded that leptin plays a role in the severity of asthma in children.⁽³⁰⁾

Our data support the hypothesis that obese patients with asthma exhibit Th1 polarization, whereas lean patients with asthma exhibit Th2 polarization, and that IFN- γ might be a pathway in the process of leptin-induced inflammation. This suggests that, in obese subjects with asthma, Th1 polarization might be modulated more by obesity and less by asthma itself, and this is supported by the lack of correlation between leptin and IFN- γ levels and between leptin and IgE levels in obese children with asthma.

We conclude that, although serum leptin is involved in the pathogenesis of asthma in obese and non-obese children, its effect is more pronounced in obese patients. In the presence of high leptin levels, only obese children with asthma exhibited Th1 polarization, with higher IFN- γ levels.

In obese children with asthma, leptin and IFN- γ aggravate and augment airway inflammation, thus increasing asthma severity. Strategies for the treatment of obese children with asthma should take these findings into consideration.

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