Original Article

Reduction in the Leptin Concentration as a Predictor of Improvement in Lung Function in Obese Adolescents

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Key Words

Obesity management · Adolescent · Adipokines · Lung function

Abstract

Objective: To assess the effects of weight loss on adipokines, asthma-related symptoms, exercise-induced bronchospasm (EIB) and lung function, and to evaluate the role of leptin and adiponectin levels on lung function after treatment in obese adolescents. **Methods:** 84 post-pubertal obese adolescents were enrolled and distributed in quartiles according to weight loss (low (<2.5 kg), low to moderate (>2.5 and <8 kg), moderate (<8 and <14 kg) and massive (<14 kg)). Body composition was measured by plethysmography, and visceral and subcutaneous fat were detected by ultrasound. Serum levels of adiponectin and leptin were analyzed. Lung function, asthma and EIB were evaluated according to the American Thoracic Society criteria. Patients were submitted to 1 year of interdisciplinary intervention consisting of physiotherapy, medical, nutritional, exercise, and psychological therapy. **Results:** After treatment the moderate and massive weight loss promoted an increase in adiponectin and adiponectin/leptin (A/L) ratio as well as a decrease in leptin levels and a reduction in EIB frequency and asthma-related symptoms. Furthermore, the reduction in leptin levels was a predictor factor to improvement in lung function. **Conclusion:** Interdisciplinary therapy was able to decrease EIB and asthma-related symptoms and to improve pro/anti-inflammatory adipokines. Additionally, the leptin concentration was a predictor factor to explain changes in lung function.

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Introduction

Obesity is an important public health problem. According to the last survey, approximately 49% of the adult Brazilian population is currently obese or overweight. In Brazilian adolescents the prevalence of obesity is also increasing and has more than doubled in the last 20 years [1]. These data reflect a general trend as the incidence of obesity is increasing progressively worldwide [2].

Several studies have documented a negative impact of obesity on lung function and/or exercise-induced bronchospasm (EIB) [3–6]. In addition, obesity has been associated with asthma in both adults and children [7–9], contributing to an increase in asthma severity [10, 11].

The mechanism for this association is unclear, but genetic, hormonal, environmental, mechanical, and immunological pathways have been suggested [12]. It is further uncertain which of these various pathways may be the dominant mechanism [13]. Two hypotheses to this relationship have been discussed in more detail: i) the mechanical effects of fat deposit are associated with diaphragm excursion and thoracic compliance [14] and ii) the second have received and involves immunological pathways and the inflammatory role of adipose tissue are involved [15], with the latter being the one receiving the greatest attention.

The obese state is characterized by increases in the serum concentrations of several pro-inflammatory cytokines such as leptin and reduced anti-inflammatory adipokines such as adiponectin [16].

Since its discovery, leptin has been described to play a central role in energy balance control [17]. However, it has another important function: up-regulation of inflammatory responses [18]. Considering the link between obesity and lung function, previous studies demonstrated that the main effects of leptin are on inflammation and lung development [13, 15, 19]. In this sense, Sood et al. [20] verified that leptin concentration was negatively correlated with lung function in adults; however, they did not explore the role of this adipokine on lung function during weight loss. On the other hand, adipocytes are the most important source of adiponectin; however, its concentration is decreased in obese subjects. Conversely, weight loss promotes an increase in adiponectin levels [21, 22]. The effects of adiponectin go beyond metabolic effects on fatty acid metabolism and glucose regulation; it also includes an anti-inflammatory effect [23–25]. In this sense, studies that associated adipokines and asthma have documented a protective effect of high adiponectin concentrations [26, 23].

Recently, the evaluation of the adiponectin/leptin (A/L) ratio has been used as a better predictor of inflammatory process and insulin resistance [21, 27, 28]. However, to our knowledge there is no study investigating the role of A/L ratio in the relationship between obesity and lung function as well as the effects of different weight loss quartiles on A/L ratio.

Previous studies have demonstrated the important role of interdisciplinary weight loss therapy in the treatment of obesity and related comorbidities [29–31]. However, the effects of different magnitudes of weight loss on lung function are not studied and thus unknown [32].

Therefore, considering the role of adipokines on lung function, and the importance of treatment strategies to control obesity and respiratory conditions, the primary objective of the present study was to evaluate adipokine levels, asthma-related symptoms, EIB frequency and lung function in accordance to magnitude of weight loss. The secondary objective was to assess how treatment-induced leptin and adiponectin concentration changes affect lung function in obese adolescents.

Fig. 1. Study protocol diagram.

Material and Methods

Population

A total of 110 adolescents (15 to 19 years old) with simple obesity (BMI > 95th percentile on the CDC reference growth charts) [33] and at the postpubertal stage on the Tanner scale (stage 5) for both boys and girls [34] were enrolled in this study (fig. 1). This study was carried out in accordance with the principles of the Declaration of Helsinki and was formally approved by the Institutional Ethical Committee of the Universidade Federal de São Paulo – UNIFESP (0135/04). Informed consent was obtained from all subjects and/or their parents, and participation of the adolescents and their families was voluntary.

The study occurred at the Sleep Institute in CEPE-GEO – Obesity Interdisciplinary Program, São Paulo. The data were obtained from patients enrolled from 2008 to 2010. Non-inclusion criteria were as follows: metabolic, endocrine or identified genetic diseases; viral diseases; previous drug use; cardiac illnesses and smoking.

Study Protocol and Medical Screening

Subjects were medically screened, and their pubertal stage and anthropometric measures were evaluated. For all subjects, the procedures were scheduled for the same time of day to preclude any influence of diurnal variation. A physician monthly recorded health and clinical parameters of the participants (fig. 1).

Anthropometric Measurements and Body Composition

Subjects were weighed while wearing light clothing and no shoes on a Filizola scale to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm with a wall-mounted stadiometer (Sanny, model ES 2030). BMI was calculated as body weight divided by height squared (kg/m^2).

Body composition was measured by plethysmography in a BOD POD body composition system (version 1.69; Life Measurement Instruments, Concord, CA, USA) [35]. Visceral and subcutaneous fat were assessed by ultrasonography as previously described [29, 36].

Serum Analysis

Blood samples were collected by a skilled and qualified technician at the outpatient clinic around 8 a.m. after an overnight fast. After collection, the blood was centrifuged for 10 min at 5,000 r.p.m. and stored at -70°C . The materials used for collection were disposable, adequately labeled, and of recognized quality. Adiponectin (Phoenix Pharmaceuticals, Belmont, CA, USA) and leptin (CHEMICON International, Inc., Millipore, Billerica, MA, USA) levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit according to the manufacturer's instructions.

Evaluation of the Lung Function

Lung function was measured with a spirometer EasyOne® model 2001 (ndd Medizintechnik AG, Zurich, Switzerland) according to American Thoracic Society (ATS) criteria [37]. The highest of three technically appropriate measurements was recorded. While performing the maneuver, volume-time and flow-volume curves were followed on the screen. Forced vital capacity (FVC; in liters), forced expiratory volume in 1 s (FEV1; in liters), FEV1/FVC (in %) and peak expiratory flow (PEF; in l/s) were measured, and predicted values were obtained [38].

The diagnosis of asthma was made according to ATS guidelines [37]. The asthmatic patients had a 6-month or longer history of recurrent chest symptoms such as coughing, dyspnea and wheezing, which were relieved by bronchodilator treatment. They also demonstrated reversible airflow limitation. The International Study of Asthma and Allergy in Childhood (ISAAC) questionnaire was used to assess asthma-related symptoms [39]. Furthermore, information on anti-asthmatic medication was obtained. The asthmatic patients were evaluated by a pulmonologist. Medical therapy included regular use of inhaled corticosteroids or β_2 -agonists (data not shown).

Tests for maximal volitional ventilation in 15 s (MVV15) were performed on a computerized spirometry system (EasyOne® model 200; ndd Medizintechnik AG) according to procedures published by the ATS [40]. The greatest value from three repeated measurements was used for subsequent analysis. During all tests of respiratory muscle performance, subjects were seated upright.

Exercise Challenge Test

A standardized exercise challenge consisted of 8 min on a treadmill and was initiated at a speed of 1 km/h and a 0% inclination, increasing by 1.5 km/h and a 2.5% inclination after each 30-second period for 2 min until a speed of 6 km/h and a level of inclination of 10% was achieved. The challenge was conducted by having patients run for 8 min while inhaling air through their mouth, at a workload that increased the heart rate to 80% of the age-predicted maximum [41]. During the days of testing, mean temperature and relative humidity were $25 \pm 5^{\circ}\text{C}$ and $41 \pm 10\%$, respectively. The study was conducted in the afternoon (1:00 to 5:00 p.m.).

Spirometric measurements were made immediately before and at 2, 5, 10, 15, 20, 25 and 30 min after exercise. To measure EIB, the maximal change in FEV1 was calculated as $100 \times ((\text{FEV1 at baseline} - \text{lowest FEV1 after exercise}) / \text{FEV1 at baseline})$. EIB diagnosis was defined as a 15% or greater reduction in FEV1 after exercise compared to FEV1 at baseline.

Research Design

The use of interdisciplinary intervention has been suggested by the World Health Organization [42]. All measurements were performed at baseline and after 1 year of therapy.

Physiotherapy

The volunteers were submitted to physical therapy evaluation at baseline. Subsequently, all subjects were accompanied by a physiotherapist during the therapy in order to prevent musculoskeletal injuries. Additionally, the volunteers had lessons regarding topics such as postural habits, prevention of musculoskeletal injuries and prevention and management of asthma symptoms and EIB occurrence. During exercise therapy, the patients with asthma were accompanied by a physical therapist who controlled their symptoms.

Table 1. Quartiles of weight loss of obese adolescents after 1 year of interdisciplinary intervention

1st (<2.5 kg)	Low
2nd (>2.5 and <8 kg)	Low to moderate
3rd (>8 and <14 kg)	Moderate
4th (>14 kg)	Massive

Nutritional Therapy

Once a week for 1 year, adolescents had nutritional lessons regarding topics such as food pyramid, food record, weight loss diets, diet and light concepts, fat and cholesterol, and eating disorders. Energy intake was set at the levels recommended by the dietary reference for subjects with low levels of physical activity of the same age and gender [43]. A 3-day dietary record was made for each adolescent to help his/her parents. Portions were measured in terms of familiar volumes and sizes. The nutritionist explained to the parents and the adolescents how to record food consumption. These dietary data were transferred to a computer by the same nutritionist, allowing for nutrient composition analysis by a PC program developed at the Universidade Federal de São Paulo (Nutwin software, for windows, 1.5 version, 2002) based on Western and local food tables.

Physical Therapy

An aerobic and resistance training regimen was performed 3 times a week for 1 year. Each session included 30 min of aerobic training plus 30 min of resistance training. Aerobic training consisted of running on a motor-driven treadmill (Life Fitness, Model TR 9700HR; São Paulo, Brazil) at the cardiac frequency intensity of ventilatory threshold I (± 4 bpm), which was determined by the results of an initial oxygen uptake test for aerobic exercise (cycle ergometer and treadmill). In addition, the maximal O₂ consumption (VO₂max) values of the oxygen uptake test were obtained.

The physiologists controlled the cardiac frequency, which was measured with a cardiometer at 5-min intervals during all training sessions (Polar, Model FS1 dark blue; Lake Success, NY, USA). The exercise program was based on the American College of Sports Medicine (ACSM) recommendations [44].

Psychological Therapy

During 1 year of interdisciplinary therapy, the adolescents received psychological orientation for 1 h in a weekly group session. A psychologist discussed body image and eating disorders as well as binge eating disorders and their signs, symptoms, and health consequences. The psychologist also discussed the relationship between emotions and food as well as familial problems in a group setting. Individualized psychological therapy was recommended if behavioral alterations including depression and anxiety symptoms or poor dietary habits such as bulimia, anorexia nervosa and binge eating became apparent [30].

Statistical Analysis

Statistical analyses were performed using STATISTICA version 7.0 for Windows StatSoft Inc., Tulsa, OK, USA). The Gaussian distribution of variables was verified with a Shapiro-Wilk's W test, and variables with normal distribution were expressed as the mean $\pm$ standard deviation (SD), while variables without normal distribution were expressed as medians (minimum and maximum) in a descriptive table. Non-parametric methods were used when appropriate.

The comparisons between the measurements of the parametric variables before and after intervention were determined by paired Student's t-tests. The Wilcoxon signed rank and Mann-Whitney U tests were used to analyze the non-parametric variables. Comparisons between groups were made using unpaired Student's t-tests (parametric variables) or the Mann-Whitney test (non-parametric variables). The chi-square test was used to evaluate gender, EIB frequency and asthma-related symptoms between the times of evaluation. Subjects were distributed in quartiles according to the magnitude of weight loss (table 1).

We assessed the correlation between Δ values of variables (Δ = the difference of values between 1 year and baseline). Pearson's correlation coefficients were calculated to assess possible relationships between normally distributed variables. For non-normal measurements, Spearman's correlation coefficients were used.

Multiple regression analysis was used to ascertain the predictor factors to changes in lung function. The lung function variables (FVC, FEV1 or PEF) were set as dependent variables in different models, and body mass, A/L ratio or leptin levels were set as independent variables; all analysis only were adjusted for weight loss quartiles and asthma diagnosis.

Furthermore, Grubb's test was used to detect outliers in data using GraphPad Prism® version 5.0 for Windows (GraphPad Software, Inc., La Jolla, CA, USA). The results were considered statistically significant at the level of $p < 0.05$.

Results

At the beginning of the therapy, 110 obese adolescents were enrolled in the program. However, only 84 patients completed 1 year of therapy with more than 75% of treatment sessions. It is important to note that there were no differences for all variables between those who completed the therapy and the last known data from those who did not. The main reasons for dropping out were financial and family problems, followed by school and job opportunities (fig. 1).

For analysis of the variables studied, the volunteers were divided in quartiles of weight loss (table 1). At baseline, we did not find significant differences in age and BMI between groups once the studied population was paired by these variables according to gender. There were no statistically significant differences between genders in the groups for all variables (data not shown).

Results of the Low Weight Loss Quartile

After 1 year of interdisciplinary intervention, low weight loss did not promote a significant reduction in any of the anthropometric and lung function variables (table 2). In addition, the low weight loss group did not present any alteration in adipokine profile and A/L ratio (table 3) and did not reduce asthma-related symptoms and EIB frequency after therapy (table 4). However, the VO2 max values increased after therapy (table 2).

Results of the Low to Moderate Weight Loss Quartile

After therapy the low to moderate weight loss group showed significantly decreased fat mass and increased fat free mass percentage. Furthermore, we observed a significant increase in lung function variables and VO2 max values (table 2). However, we did not observe any alteration in adipokines profile and A/L ratio (table 3). On the other hand, asthma-related symptoms after therapy were reduced in these subjects (table 4).

Results of the Moderate Weight Loss Quartile

The moderate weight loss promoted a significant reduction in all anthropometric variables and a significant increase in lung function variables and VO2 max values (table 2). Moreover, an increase in adiponectin concentration as well in A/L ratio and a decrease in leptin concentration after therapy could be demonstrated (table 3). In addition, the subjects in the moderate weight loss quartile presented with higher frequency of EIB than those of the fourth quartile at baseline. Nevertheless, the asthma-related symptoms and EIB frequency were reduced after therapy (table 4).

Results of the Massive Weight Loss Quartile

In the massive weight loss group, a significant reduction in all anthropometric variables and a significant increase in lung function variables and VO2 max values were observed after therapy (table 2). Indeed, it could be shown that the massive weight loss promoted an

Table 2. Anthropometric, subcutaneous and visceral adipose tissues, V02 max values and lung function variables according quartiles of weight loss at baseline and after 1 year of interdisciplinary intervention

Variables	1st (<2.5 kg weight loss) (n = 17)		2nd (≥2.5 kg and <8 kg weight loss) (n = 24)		3rd (≥8 kg and <14 kg weight loss) (n = 22)		4th (≥14kg weight loss) (n = 21)	
	baseline	1 year	baseline	1 year	baseline	1 year	baseline	1 year
Female, %	50		70		58		58	
Body mass, kg	105 ± 18	105 ± 19	99 ± 16	94 ± 18	110 ± 18	99 ± 19 ^a	111 ± 12	89 ± 12 ^a
BMI, kg/m ²	36 ± 6	35 ± 7	36 ± 5	34 ± 5	39 ± 5	35 ± 7 ^a	39 ± 5	31 ± 4 ^a
Fat mass, %	43 ± 8	40 ± 8	46 ± 5	40 ± 6 ^a	49 ± 6	40 ± 9 ^a	47 ± 6	35 ± 8 ^a
Fat free mass, %	57 ± 8	60 ± 8	54 ± 5	60 ± 6 ^a	51 ± 6	60 ± 9 ^a	53 ± 5	64 ± 8 ^a
Visceral fat, cm	4.6 ± 1.8	3.4 ± 1.9	4.1 ± 1.2	3.0 ± 1.6	4.6 ± 1.8	2.3 ± 0.7 ^a	4.5 ± 1.3	2.8 ± 1.3 ^a
Subcutaneous fat, cm	3.9 ± 0.7	3.7 ± 0.5	3.9 ± 0.6	3.4 ± 0.5	4.2 ± 1.0	3.2 ± 1.0 ^a	4.1 ± 1.0	2.9 ± 0.7 ^a
Lung function variables								
FVC, %	98 ± 8	105 ± 10	93 ± 9	106 ± 12 ^a	94 ± 9	113 ± 12 ^a	93 ± 9	120 ± 10 ^{a,d,f}
FEV1, %	90 ± 11	99 ± 11	87 ± 9	101 ± 12 ^a	83 ± 10	103 ± 15 ^a	85 ± 7	117 ± 10 ^{a,d,f}
FEV1/FVC, %	97 ± 11	101 ± 5	91 ± 12	97 ± 7	87 ± 13	91 ± 9	92 ± 13	98 ± 7
PEF, %	93 ± 15	101 ± 15	82 ± 10	97 ± 11 ^a	85 ± 14	100 ± 13 ^a	86 ± 11	114 ± 11 ^a
MVV, %	83 ± 8	106 ± 21	81 ± 15	103 ± 16 ^a	77 ± 11	101 ± 17 ^a	82 ± 9	108 ± 13 ^a
V02max, ml/kg/min	23 ± 4	28 ± 11 ^a	25 ± 5	27 ± 7 ^a	27 ± 4	29 ± 6 ^a	25 ± 7	28 ± 7 ^a

MVV = Maximum voluntary ventilation; FVC = forced vital capacity; FEV1 = forced expiratory volume 1 s; PEF = peak expiratory flow. ^aDifference between baseline and 1 year. ^bDifference between 1st and 2nd quartiles at the same time. ^cDifference between 1st and 3rd quartiles at the same time. ^dDifference between 1st and 4th quartiles at the same time. ^eDifference between 2nd and 3rd quartiles at the same time. ^fDifference between 2nd and 4th quartiles at the same time. ^gDifference between 3rd and 4th quartiles at the same time.

Table 3. Cytokines data of obese adolescents according to quartiles of weight loss at baseline and after 1 year of interdisciplinary intervention

Variables	1st (<2.5 kg weight loss) (n = 17)		2nd (≥2.5 kg and <8 kg weight loss) (n = 24)		3rd (≥8 kg and <14 kg weight loss) (n = 22)		4th (≥14 kg weight loss) (n = 21)	
	baseline	1 year	baseline	1 year	baseline	1 year	baseline	1 year
Adiponectin, µg/ml (range)	6 (1.7–8)	5 (4–13)	6 (0.2–15)	6 (3–16)	8 (1.9–13)	10 (2–16) ^a	6 (3–14)	10 (3–22) ^{ab}
Leptin, ng/ml (range)	24 (21–99)	24 (19–95)	33 (5–100)	31 (17–99)	24 (1.2–65)	23 (3.3–58) ^a	38 (14–61) ^d	25 (3–46) ^a
A/L ratio (range)	0.23 (0.0–0.34)	0.20 (0.0–0.53)	0.15 (0.0–8.5)	0.12 (0.0–0.9)	0.31 (0.0–3.6)	0.33 (0.0–6.5) ^a	0.21 (0.1–0.5)	0.45 (0.1–6.0) ^{adf}

^aDifference between basal and 1 year. ^bDifference between 1st and 2nd quartiles at the same time. ^cDifference between 1st and 3rd quartiles at the same time. ^dDifference between 1st and 4th quartiles at the same time. ^eDifference between 2nd and 3rd quartiles at the same time. ^fDifference between 2nd and 4th quartiles at the same time. ^gDifference between 3rd and 4th quartiles at the same time.

Table 4. Asthma, symptoms and EIB frequency data of obese adolescents according to quartiles of weight loss at baseline and after 1 year of interdisciplinary intervention

Variables	1st (<2.5 kg weight loss) (n = 17)		2nd (≥2.5 kg and <8 kg weight loss) (n = 24)		3rd (≥8 kg and <14 kg weight loss) (n = 22)		4th (≥14 kg weight loss) (n = 21)	
	baseline	1 year	baseline	1 year	baseline	1 year	baseline	1 year
Asthma frequency, %	14		35		63 ^c		24	
EIB frequency, %	57	29	88	59	81	31 ^a	29 ^g	5 ^a
Asthma-related symptoms, %	14	10	35	20 ^a	63 ^c	10 ^{a,c}	24	9 ^a
Daily rescue medication doses in asthmatics patients (range)	2 (1.5–2.5)	2 (1.0–2.5)	2 (1.0–2.5)	1 (0.5–2.0)	2 (1.5–2.5)	1 (0.5–1.5)	2 (1.0–2.5)	1 (0–1.5)

^aDifference between basal and 1 year. ^bDifference between 1st and 2nd quartiles at the same time. ^cDifference between 1st and 3rd quartiles at the same time. ^dDifference between 1st and 4th quartiles at the same time. ^eDifference between 2nd and 3rd quartiles at the same time. ^fDifference between 2nd and 4th quartiles at the same time. ^gDifference between 3rd and 4th quartiles at the same time.

Fig. 2. Correlation coefficients between delta of FVC and delta of **A** BMI, **B** Δ leptin and **C** Δ A/L ratio after 1 year of intervention.

increase in adiponectin and A/L ratio and a decrease in leptin concentrations after therapy. On the other hand, higher values of leptin were observed in the fourth quartile compared to the low weight loss quartile at baseline (table 3). The asthma symptoms as well as EIB frequency were reduced after massive weight loss (table 4).

Results of All Analyzed Patients

The absolute value of changes after therapy in FVC exhibited a negative correlation with BMI ($r = -0.54$, $p = 0.000$) and leptin concentration ($r = -0.44$, $p = 0.001$) and were positively correlated with A/L ratio ($r = 0.36$, $p = 0.000$) (fig. 2). Furthermore, the changes in FEV1 were negatively correlated with BMI ($r = -0.57$, $p = 0.001$) and leptin concentration ($r = -0.41$, $p = 0.000$), but positively correlated with A/L ratio ($r = 0.33$, $p = 0.001$) (fig. 3). In addition, Δ PEF was negatively correlated with BMI ($r = -0.34$, $p = 0.001$) and leptin concentration ($r = -0.37$, $p = 0.000$) (fig. 4).

As shown in table 5, multiple linear regression analysis demonstrated that Δ leptin concentration was an independent factor to changes in FVC, FEV1 and PEF values in obese adolescents. Furthermore, Δ BMI was an independent predictor to changes only for the FEV1 values.

Fig. 3. Correlation coefficients between Δ FEV₁ and **A** Δ BMI, **B** Δ leptin and **C** Δ A/L ratio after 1 year of intervention.

Discussion

Previous studies demonstrated the important role of interdisciplinary therapy in the treatment of obesity [22, 29–31]. However, the influence of this kind of therapy according to magnitude of weight loss on lung function, asthma-related symptoms, and EIB had not been studied yet. It could be demonstrated in our study that 1 year of interdisciplinary therapy was able to improve lung function and to decrease asthma-related symptoms and EIB frequency, which is paralleled by an improvement in pro/anti-inflammatory adipokine profile in obese adolescents with moderate and massive weight loss.

Obesity negatively affects several respiratory physiologic parameters such as compliance, lung volume and airway responsiveness [14]. The mechanisms underlying these effects are likely to be complex and may include mechanical effects of central fat deposit on the diaphragm and the chest wall that would cause a reduction in diaphragm excursion and consequently a decrease in thoracic compliance and lung volumes limiting the expansion of the lungs [32, 45] as well as inflammatory processes related to adipose tissue release of

Fig. 4. Correlation coefficients between delta of PEF and **A** Δ BMI and **B** Δ leptin after 1 year of intervention.

Table 5. Multiple regression analysis for the determinants of changes in FVC, FEV1 or PEF

Independent variable	Δ FVC		Δ FEV1		Δ PEF	
	B coefficient	p value	B coefficient	p value	B coefficient	p value
Δ BMI*	-1.53	0.51	-2.05	0.009	-1.02	0.158
Δ Leptin*	-0.36	0.007	-0.62	0.000	-0.31	0.038
Δ Adiponectin/leptin ratio*	2.67	0.43	1.58	0.63	2.35	0.40

*Analyses are adjusted only for weight loss quartiles and asthma diagnosis.

adipokines, which possess anti-inflammatory effects, e.g. adiponectin, or pro-inflammatory properties, e.g. leptin [13, 15].

One of the main findings in the present investigation was that leptin concentration reduction was a predictor factor for improvements in FVC, FEV1 and PEF, while the Δ BMI was predictor factor only for FEV1. These findings suggest a close association between leptin and lung function, which can be explained by the effects of leptin on inflammation and lung development [26].

Leptin has pro-inflammatory properties as it stimulates the release of pro-inflammatory cytokines such as IL-6 and TNF- α from the adipose tissue [46] and a negative modulatory effect on regulatory T cells. Accordingly, previous studies have demonstrated that leptin concentrations are increased during allergic reactions in the airways [47] and play a role in the intrauterine, neonatal, and post-natal lung development [47, 48]. Moreover, leptin concentrations are increased in obese subjects, including adolescents [17, 49]. Thus, it is important to note that in the present study a decrease in leptin concentration after moderate and massive weight loss could be observed, but 1 year of treatment was not able to normalize the leptin values. Thus, our results and data from literature corroborate the hypothesis that leptin plays a central role in inflammatory processes linking obesity and pulmonary diseases.

Another important result in the present study was that adiponectin concentration and A/L ratio significantly increased after moderate and massive weight loss, a finding which was in agreement with previous studies [21, 22]. The anti-inflammatory adipokine adiponectin is one of most abundant gene products in adipose tissue. It has been shown to promote a protective effect in asthma [23, 26]. The anti-inflammatory effects of adiponectin include inhibition of pro-inflammatory cytokines such TNF- α and IL-6, as well as stimulation of anti-inflammatory cytokines such IL-10 and IL-1 receptor antagonist [50].

A positive association between change in A/L ratio and lung function was shown in the present investigation, reinforcing the importance of studying the role of pro/anti-inflammatory adipokines in the control of obesity and respiratory diseases. In addition, the increase in A/L ratio after therapy is in agreement with the results of a previous study on obese adolescents boys [21]. According to Inoue et al. [27], this increase in A/L ratio may reflect enhanced insulin sensitivity and a reduced cardiovascular risk of the obese adolescents.

Previous studies on obese subjects have demonstrated that the decrease in EIB frequency after weight loss was accompanied by an improvement in lung function [51, 52]. However, these studies did not relate the decreased frequencies of EIB to the magnitude of weight loss. One important finding of our investigation was that moderate and massive weight loss, resulted in a reduction of asthma-related symptoms and EIB frequency, suggesting that a reduction of 10–20% (11–21 kg) in body mass was necessary to affect EIB prevalence in our patients. Aaron et al. [53] were able to show that a weight loss ≥ 20 kg in women receiving restricted calorie diet improved lung function and reduced asthma-related symptoms but did not influence airway responsiveness.

Obese subjects showed an increased EIB frequency when compared with lean individuals [4–6]. Moreover, EIB might be a restriction to practice physical exercise and thus contribute to sedentarism, thus being part of the vicious circle of causes and consequences linking obesity and respiratory conditions [54]. Reduction of EIB frequency, therefore, might be an important cornerstone in the integrated clinical approach to control both obesity and respiratory conditions.

One limitation of our study is the lack of a control group. However, it should be mentioned that the primary objectives of the present study were to assess the effects of weight loss magnitude and how lung function is affected by changes in pro/anti-inflammatory adipokine levels.

In conclusion, the leptin concentration could be identified as an predictor factor to explain changes in lung function. Furthermore, moderate and massive weight loss was accompanied by a reduction in EIB frequency and asthma-related symptoms resulting in an improvement of lung function in obese adolescents submitted to 1 year of interdisciplinary weight loss therapy.

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Ethical Approval

Project approval was obtained from Human Research Ethics Committee of Universidade Federal de São Paulo – UNIFESP (0135/04).

Disclosure Statement

The authors have disclosed no conflicts of interest.

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