

TITLE PAGE**Effects of weight loss on dynamic hyperinflation in women obese asthmatics****Name of authors:**

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Running head: Effects of weight loss on DH in obese asthmatics

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ABSTRACT

Obese adults with asthma are more likely to develop dynamic hyperinflation (DH) and expiratory flow limitation (EFL) than non-obese asthmatics, and weight-loss seems to improve the breathing mechanics during exercise. However, studies evaluating the effect of weight-loss on DH in obese adults with asthma have not been performed. **Objective:** To evaluate the effect of a weight-loss program on DH in obese adults with asthma. **Methods:** Forty-two asthma patients were enrolled in a weight-loss program (diet, psychological support and exercise) and were subsequently divided into two groups according to the percentage of weight-loss: the $\geq 5\%$ group (n=19) and the $< 5\%$ group (n=23). Before and after the intervention, DH and EFL (constant load exercise), health-related quality of life (HRQoL), asthma control, quadriceps muscle strength and endurance, body composition and lung function were assessed. **Results:** Both groups exhibited a decrease of $\geq 10\%$ in inspiratory capacity (DH) before intervention, and only the $\geq 5\%$ group showed clinical improvement in DH compared to $< 5\%$ group post-intervention ($-9.1 \pm 14.5\%$ vs. $-12.5 \pm 13.5\%$, respectively). In addition, the $\geq 5\%$ group displayed a significant delay in the onset of both DH and EFL and a clinically significant improvement in HRQoL and asthma control. Furthermore, a correlation was observed between reduced waist circumference and increased inspiratory capacity ($r = -0.45$, $p = 0.05$) in the $\geq 5\%$ group. **Conclusion:** A weight-loss $\geq 5\%$ of the body weight improves DH, which is associated with waist circumference in obese adults with asthma. In addition, the group with greater weight-loss showed a delayed onset of DH and EFL during exercise and improved asthma clinical control and HRQoL.

Keywords: asthma, obesity, weight loss, dynamic hyperinflation, expiratory flow limitation.

NEW & NOTEWORTHY

This is the first study to evaluate dynamic hyperinflation (DH) after a weight loss program in obese patients with asthma. Our results demonstrate that a moderate weight loss can improve DH in obese patients with asthma that is associated with a decrease in abdominal fat. Moreover, a minimum of 5% in weight loss delays the onset of DH and expiratory flow limitation beside induced a clinical improvement in asthma quality of life and clinical control.

INTRODUCTION

Asthma is a complex, heterogeneous disease characterized by chronic airway inflammation, and it is best understood in terms of the underlying phenotypes (22). Recently, studies have identified a distinct asthma phenotype associated with obesity that occurs predominantly in women and is characterized by more severe symptoms, variable response to conventional therapies, poorer quality of life and reduced lung function compared to those of other phenotypes (40,53). Obesity increases the difficulty of asthma management through multiple mechanisms, which involve inflammatory, immunological and mechanical factors (13). Asthma and obesity lead to a decrease in lung volumes that affects ventilatory function. This limitation is even worse during exercise when the expiratory flow limitation (EFL) increases, causing a temporary increase in the end-expiratory lung volume (EELV) that is defined as dynamic hyperinflation (DH) (24).

The increase in the EELV during exercise can also be explained by a reduction in the operating lung volume resulting from weight-related mechanical forces on the chest wall (37,50). Therefore, obese asthma patients have more frequent and intense occurrences of DH than non-obese asthma patients because they breathe at lower lung volumes with increased EFL and respiratory rates (16). Previous studies have shown that DH may increase dyspnea and exercise limitations in patients with chronic airflow limitation (7) and reduce exercise capacity in non-obese asthma patients (45). Additionally, Ferreira and coworkers observed that only the quadriceps endurance was predictive of exercise tolerance, which is a consequence of a sedentary lifestyle and changes in the peripheral muscle rather than airflow limitations and DH (16).

Prior investigations have shown the positive effects of weight loss in obese asthma patients on several outcomes, such as clinical control (17,46,49), asthma symptoms (25,51), lung volume (12,17,25,46), health-related quality of life (12,36,46,49) and airway hyperresponsiveness (46). However, the effect of weight loss on breathing mechanics in obese asthma patients remains unclear. Evidence has shown that modest weight loss improves respiratory function during

submaximal exercise in healthy obese subjects, which seems to be related to the cumulative loss of chest wall fat (2). These changes in breathing load could also have positive effects on exercise endurance and adherence to physical activity in healthy obese women (4).

To the best of our knowledge, no previous studies have evaluated the effect of weight loss on dynamic hyperinflation in obese asthmatics. Obese adults with asthma are more likely to develop DH, and weight loss seems to improve breathing mechanics during exercise. Then, we hypothesized that weight loss could reduce the restriction in the rib cage imposed by excess fat mass, with a consequent increase in expiratory reserve volume and functional residual capacity, avoiding air trapping and thus decreasing DH in obese asthmatic patients. The aim of this study was to assess the effect of weight loss on DH in obese asthma patients. The secondary aims were to evaluate the effect of weight loss on EFL and to evaluate the association between DH and changes in body composition and pulmonary function.

METHODS

Subjects

Fifty-one grade II obesity women with asthma ($\text{BMI} \geq 35$ and $<40 \text{ kg/m}^2$) between 30 and 60 years of age were recruited from an outpatient asthma clinic at a university hospital. All patients who met the following inclusion criteria were invited to participate in the study: (i) moderate to severe persistent asthma diagnosed based on the Global Initiative for Asthma (20); (ii) medical treatment for at least 6 months before the study; (iii) clinically stable (i.e., no hospitalizations or visit to the emergency care or medication changes for ≥ 30 days); (iv) asthma-optimized drug therapy use (21); and (v) a forced expiratory volume in the first second (FEV_1) $\geq 60\%$ of the predicted volume. Patients were excluded if they met the following criteria: (i) the presence of cardiovascular, musculoskeletal, neurological or other chronic pulmonary diseases that would impair any assessment; (ii) weight loss $>5\%$ and/or anti-obesity drug use within the past 6 months; (iii) history

of bariatric surgery; (iv) regular use of oral corticosteroids; (v) uncontrolled hypertension or diabetes; (vi) active cancer; (vii) participation in another research protocol or inability to understand the questionnaires; (viii) smokers or ex-smokers (≥ 10 pack-years); (ix) pregnancy and (x) psychiatric problems. The Hospital Ethics Committee approved the study (07137512.9.0000.0068), and all patients provided written informed consent before participating.

Study design

The subjects were evaluated on 3 non-consecutive days. On the first visit, anthropometric indices (weight, height, body mass index (BMI) and waist circumference), body composition and quadriceps muscle strength and endurance were evaluated. On the second visit, the patients reported their clinical control of asthma using the Asthma Control Questionnaire (ACQ) and underwent cardiopulmonary exercise testing and the pulmonary function test. On the third visit, dynamic pulmonary hyperinflation and expiratory flow limitation during physical exercise were assessed through submaximal exercise (75% of the maximum exercise capacity obtained during the cardiopulmonary exercise test) (44). All these evaluations were performed before and after the intervention program (17).

Measurements

Anthropometric data and body composition

The anthropometric data (weight and height) were measured using a stadiometer (Filizola, Brazil) according to standard protocols (23), and waist circumference was measured with a tape measure. BMI was calculated as the ratio of weight (in kilograms) to height (in meters) squared (6). Body composition (fat mass, lean mass, fat-free mass and visceral fat area) was evaluated by eight-point bioelectrical impedance (InBody720; Biospace, Seoul, South Korea) (19) according to the standard protocol (19).

Asthma control

The Asthma Control Questionnaire (ACQ) (34), validated for Brazilian Portuguese (35), was used to assess the clinical control of asthma. The ACQ has five questions related to asthma symptoms (daytime and nocturnal asthma symptoms, activity limitations, dyspnea, wheezing), a question about rescue bronchodilator use (short-acting B2-agonist) within the last week and a question about pulmonary function (forced expiratory volume in 1 second (FEV₁) in % predicted, pre-bronchodilator) (34). The responses range between 0 and 6 points, and the overall score is the mean value of the responses (0=totally controlled, 6=severely uncontrolled). Values greater ≥ 1.5 indicate uncontrolled asthma; values between 0.75 and 1.5 indicate partially controlled asthma; and values < 0.75 indicate fully controlled asthma (30).

Asthma health-related quality of life

Asthma health-related quality of life was assessed using the Asthma Quality of Life Questionnaire (AQLQ) (31,32), which includes four domains: activity limitations (AL), symptoms (S), emotional function (EF) and environmental stimuli (ES). Higher AQLQ scores indicate greater quality of life, and clinically effective treatment results in a 0.5-point increase in the score following the intervention (33).

Pulmonary function test

Spirometry and lung volumes and capacities were obtained using a calibrated whole-body plethysmograph (Medical Graphics Corporation, MN, USA). The following variables were obtained: functional residual capacity (FRC), expiratory reserve volume (ERV), residual volume (RV), inspiratory capacity (IC) and total lung capacity (TLC), FEV₁, forced vital capacity (FVC), FEV₁/FVC ratio and bronchodilator response according to ATS/ERS recommendations (39, 56). Predicted values were obtained from the Brazilian population results for lung function tests (42) and forced spirometry (48).

Cardiopulmonary exercise testing (CPET)

The CPET was performed using a cycle ergometer (Corival, Lode B.V.; Medical Technology, GN, NL) linked to a gas analysis system (CardioO₂ System; Medical Graphics Corporation, MN, USA). The incremental exercise protocol consisted of 2 minutes of rest, followed by 2 minutes of warm-up and the incremental test. The work rate was set between 10 and 20 W/min according to the patient's daily life physical activity, targeting a CPET duration between 8 and 12 minutes (57). During the test, the patients were instructed to maintain constant pedaling at 60 rpm. Peripheral oxygen saturation (SpO₂) measured by pulse oximetry (Onyx, model 9500; Nonin, Plymouth, MN, USA) and electrocardiography were monitored (Welch Allyn CardioPerfect, NY, USA). The following variables were recorded: peak exercise work rate (W), using the calculated load for the submaximal test, and peak oxygen uptake (VO₂), using the sample's baseline characteristics. In addition, blood pressure and modified Borg scales for leg discomfort and dyspnea were evaluated at rest and every 2 minutes until the peak exercise work rate was reached (5). Tests were performed as recommended by the American Thoracic Society. Predicted CPET values were calculated for the Brazilian population (43).

Submaximal exercise testing and inspiratory capacity maneuver

A submaximal cycle ergometer test at 75% of the maximum Wattage achieved during the CPET (75% CPET) and a sequence of inspiratory capacity (IC) maneuvers were performed to identify DH (44). After a 2-minute rest, the total load (75% CPET) was increased progressively over 2 minutes and maintained to exhaustion (9). The patients were asked to perform the maximal IC maneuver every 2 min (from rest to peak exercise). The baseline IC was obtained on the same day and immediately before the submaximal exercise test. Before the IC maneuver, each patient was instructed to calmly breathe through a mouthpiece while wearing a nose clip. Three acceptable IC maneuvers (a mean coefficient of variation for IC of 5%) were obtained, and the best value was

considered the baseline, as previously described (39,47). An interval of at least one minute was allowed between the maneuvers, and a minimum of four stable breaths was required before each IC maneuver. Assuming that TLC remains constant during exercise, variations of at least 10% from the baseline IC were considered to determine DH (52). The degree of expiratory flow limitation (EFL) was determined and expressed as the percentage of the tidal volume ($\%V_T$) (obtained from the exercise flow-volume loops) equal to or higher than the expiratory boundary of the maximal flow-volume envelope using the overlap method (28).

Peripheral muscle strength and endurance

The muscle strength of the quadriceps muscle in the dominant lower limb was evaluated using a load cell (EMG System, Brazil), as previously described (26). Patients were asked to sustain maximum force for 5 seconds with verbal encouragement. Five tests were performed, and the 3 tests with the highest values and less than 10% variation among them were considered. The isometric force is expressed as the percentage of the predicted values calculated from the regression predictive values, as previously proposed (26). After maximal isometric strength force was established, a quadriceps endurance test was performed. The patient was positioned in a chair with 90° flexion for knee extension and asked to perform a set of repetitions until exhaustion using 50% of the maximal load obtained in the strength test. The task was discontinued when the patient discontinued the assessed movement or stopped voluntarily (55).

Airway and systemic inflammation

Airway inflammation was quantified using the exhaled fraction of nitric oxide (FeNO) measured with a portable analyzer in accordance with ATS/ERS guidelines (14). Systemic inflammatory mediators were quantified using blood-based biomarkers. Patients were instructed to fast and not drink alcohol or caffeine for 12 hours preceding blood collection. Venous blood samples were centrifuged, and the supernatants were frozen in aliquots stored at - 80°C and analyzed at the end of

the study. The cytometric bead array method (BD Biosciences, San Jose, CA, USA) was used to analyze the levels of IL-2, IL-4, IL-5, IL-10, and vascular endothelial growth factor (VEGF) using a high sensitivity kit. Serum leptin and adiponectin levels (Millipore Corporation, St. Charles, Missouri, USA) were analyzed by ELISA, C-reactive protein (Roche/Hitachi cobas c systems) was analyzed via turbidimetry and 25-hydroxy-vitamin D levels (Beckman Coulter) were analyzed via chemiluminescence using the Unicell DxI 800 Access Immunoassay System.

Intervention program

All patients were enrolled in a weight-loss program that was composed of nutritional orientation, psychology support and an exercise program including stretching, aerobic and resistance exercises. The exercise program was performed twice a week for 3 months. After the program, the patients were divided according to their weight loss: the $\geq 5\%$ group included those who lost 5% or more of their weight, and the $< 5\%$ group included those who lost less than 5% of their weight.

Data analysis

Data normality was evaluated using the Kolmogorov-Smirnov test. The comparison of the initial categorical variables between the groups and the analysis of the difference between proportions of individuals were performed using the chi-square or Fisher test. For comparisons of the initial continuous variables between the groups, an unpaired T test or Mann-Whitney test was used. Treatment-by-time interactions were analyzed via two-way repeated measures of variances followed by a Holm Sidak post hoc test. The Pearson and Spearman correlation tests were used to evaluate the association between the variables dynamic hyperinflation, body composition, changes in body weight and lung function, with $r \leq 0.40$ (weak), $r \geq 0.40$ and < 0.7 (moderate), and $r = 0.70$ to 1 (strong). The level of significance was set at 5% ($p \leq 0.05$). All analyses were performed using statistical software (SigmaStat 3.5; Systat Software, Inc.; IL, USA).

RESULTS

Baseline characteristics

The study included 51 patients; 9 patients were lost due to non-asthma-related health problems (n=4), family problems (n=1), or changes in work (n=1) or because they did not perform all the final assessments despite several telephone calls (n=3). Therefore, 42 asthmatic patients completed the study protocol. These patients were divided into two groups for data analysis according to the percentage of weight loss: those who lost $\geq 5\%$ of their body weight ($\geq 5\%$ group; n=19) and those who lost $< 5\%$ ($< 5\%$ group; n=23). Before the intervention, both groups presented similar baseline anthropometric data, medication use, lung function, bronchodilator response, clinical control, aerobic capacity and comorbidities ($p > 0.05$, Table 1). The patients had a mean age of 47.4 ± 7.8 years, had grade II obesity (BMI of $37.9 \pm 2.5 \text{ kg/m}^2$) and presented a reduction in lung function (ERV $26 \pm 23\%$ of predicted) (Table 1).

** * Insert Table 1 * **

Dynamic hyperinflation and expiratory flow limitation

Before the intervention, the patients in both groups had similar durations for the submaximal exercise test (average of 10 minutes; $p > 0.05$) and similar dynamic hyperinflation after the test (Figure 1; $p > 0.05$). In addition, the patients in both the $\geq 5\%$ group and the $< 5\%$ group presented an expiratory flow limitation (EFL) at the end of the exercise test ($65.4 \pm 18.4\%$ vs. $62.4 \pm 22.0\%$, respectively; $p > 0.05$). After the intervention, the mean percentage change in the IC was significantly lower in the $\geq 5\%$ group compared with the baseline (Figure 1); however, the difference between the $\geq 5\%$ group and the $< 5\%$ group after the intervention was not significant ($-9.1 \pm 14.5\%$ vs. $-12.5 \pm 13.5\%$, respectively; Figure 1; $p > 0.05$). In addition, the $\geq 5\%$ group presented a similar EFL to the $< 5\%$ group ($61.6 \pm 18.8\%$ vs. $59.7 \pm 27.3\%$; $p > 0.05$). Patients in the $\geq 5\%$ group

who continued to present DH after intervention showed a delayed onset of both DH (Figure 2A) and EFL (Figure 2B) compared with patients in the <5% group ($p \leq 0.05$).

Before the intervention, both groups presented similar tidal volume and respiratory rates at the peak of the exercise (1.5 ± 0.3 L and 36 ± 9 breaths/min in the $\geq 5\%$ group vs. 1.4 ± 0.3 L and 34 ± 6 breaths/min in the <5% group, respectively; $p > 0.05$). After the intervention, the patients in the $\geq 5\%$ group presented a significant increase in tidal volume at the peak of the exercise test compared to baseline values (1.6 ± 0.3 L vs. 1.4 ± 0.3 L, respectively; $p = 0.01$), but there was no significant difference between the groups. No difference between groups was observed in the respiratory rate (37 ± 7 breaths/min in the $\geq 5\%$ group vs. 37 ± 6 breaths/min in the <5% group; $p > 0.05$).

*** Insert Figure 1 ***

*** Insert Figure 2A and 2B ***

Health-related quality of life (HRQoL) and asthma control

Before the intervention, both groups presented similar HRQoL and asthma control; however, after the intervention, the group that lost $\geq 5\%$ of their weight presented a clinically significant improvement in all domains of the AQLQ and the ACQ (change > 0.5 in the scores of both questionnaires). In addition, the $\geq 5\%$ group presented a significant difference in the AQLQ domains activity limitations, symptoms and total scores compared with the <5% group ($p < 0.05$; Table 2). However, no significant difference in the ACQ score was observed between groups after the intervention ($p > 0.05$; Table 2).

*** Insert Table 2 ***

Body composition

After 3 months of intervention, the mean percentage of weight loss in the $\geq 5\%$ group was significantly higher than that in the $< 5\%$ group ($-7.9\% \pm 2.2\%$ vs. $-2.3\% \pm 2.0\%$, respectively; $p < 0.001$). In addition, the $\geq 5\%$ group presented a greater decrease in waist circumference than the $< 5\%$ group ($p < 0.05$; Table 3). The patients in both groups showed reductions in fat mass, body fat percentage, trunk fat mass and visceral fat area; however, the reduction in all of these variables was significantly higher in the $\geq 5\%$ group ($p < 0.01$; Table 3).

** * Insert Table 3 * **

Pulmonary function and muscle strength

Both groups presented similar pulmonary function, quadriceps muscle strength and endurance before intervention, and there was no difference between the groups ($p > 0.05$; Table 4). Additionally, the patients in both groups presented air trapping before and after the intervention, and there was no difference between the groups (Table 4).

** * Insert Table 4 * **

Airway and systemic inflammation

After the intervention, only the $\geq 5\%$ group presented a significant decrease in airway inflammation (Fe_{NO}), as well as the inflammatory biomarkers (IL-2, IL-4), and increased proteins (VEGF) and anti-inflammatory biomarkers (IL-10). In addition, the $\geq 5\%$ group presented increased levels of Vitamin D compared with the $< 5\%$ group (Table 5).

** * Insert Table 5 * **

Associated variables and possible mechanisms

Linear correlation analysis was performed for body composition and change in inspiratory capacity. A moderate negative linear correlation was observed between waist circumference and inspiratory capacity in the $\geq 5\%$ group ($r=-0.45$; $p=0.05$), while no association was observed for the $<5\%$ group ($r=0.01$; $p>0.05$; Figure 3). In addition, we found a moderate negative linear correlation between IC and trunk fat mass in the $\geq 5\%$ group ($r=-0.44$; $p=0.05$), while no association was observed in the $<5\%$ group ($r=0.08$; $p>0.05$).

** * Insert Figure 3 * **

DISCUSSION

The major finding of the present study is that obese patients with asthma who lost at least 5% of their body weight presented a clinically relevant improvement in dynamic hyperinflation during submaximal exercise after intervention. In addition, they presented a delay in the onset of both DH and EFL during the submaximal exercise test and an improvement in health-related quality of life (HRQoL). The group that lost more weight also presented a decrease in fat mass, body mass index and waist circumference. Finally, the reduction in circumference may partially explain the reduction in dynamic hyperinflation. These results suggest that a minimum decrease of 5% in body weight is required to improve respiratory mechanics during exercise in obese patients with asthma.

At baseline, 70% of our obese patients with moderate to severe asthma presented dynamic hyperinflation, a result that is quite similar to those described by Ferreira and coworkers (72.2%) (16). Previous studies have also shown that both asthma and obesity are generally associated with DH (15,16,38,58), which is reflected by a progressive increase in the end-expiratory lung volume (EELV) above the relaxation volume of the respiratory system. Ofir et al. (45) reported that obese

women presented dynamic hyperinflation at the peak of exercise (16% IC reduction) that occurred due to the combination of a decrease in the time constant for lung emptying and an increase in the respiratory rate, which reduced the expiratory time. If obesity is related to DH, weight loss may have a positive effect on breathing mechanisms. Therefore, our results demonstrated that 5% of body weight represents the minimum cut-off value for achieving clinically significant improvement in the IC variation ($\leq -10\%$) (52). Babb et al. (2) suggested that a weight loss of 7% of the body weight was required to improve respiratory mechanics in obese non-asthmatic men during exercise. However, they explained this improvement by the displacement of the tidal flow-volume loop with exercise progression to a better position within the maximal flow-volume envelope, which minimized the potential risk of developing EFL during exercise (2). In contrast, Bhammar et al. (4) noted that it was not clear in their study whether weight loss would change EELV in obese women; however, it is plausible that the increase in tidal volume may be due to decreased fat in the chest wall. In the present study, obese patients with asthma presented a reduction of more than 10% in the IC, but they continued to present EFL. The difference between our results and those of Babb et al. and Bhammar et al. can be explained by the studied populations. The studies by Babb et al. and Bhammar et al. included obese non-asthmatic, while our population was composed of obese asthmatic women with greater air trapping at rest. Another possible explanation is that the reduction in FRC is partly responsible for the increase in airway resistance observed in obese individuals (59); consequently, the patients of the present study may have continued to present EFL because there was no improvement in FRC, which caused them to continue to breathe at low lung volumes.

We speculate that the clinical improvement in DH found in $\geq 5\%$ group may have occurred through two different mechanisms. First, weight loss may have improved diaphragmatic mobility by decreasing the restriction of the rib cage imposed by adipose tissue. This hypothesis is supported by a moderate negative linear correlation between the reduction in dynamic hyperinflation (change in the IC) with both the reduction in waist circumference and in the trunk fat mass. According to this

hypothesis, there should also be a correlation between Δ IC and Δ waist circumference in the $<5\%$ group. However, no correlation was observed, and this occurred because 9 of 23 patients (39.1%) either did not present a reduction in the waist circumference or they presented a small increase (3 cm) (Figure 3). In contrast, only 2 of 19 patients (10.5%) did not present a reduction in the waist circumference in the $\geq 5\%$ group. A second possible explanation for the clinical improvement in DH in the $\geq 5\%$ group may be the reduction either in the airway inflammation or in the inflammatory biomarkers secondary to weight loss (Table 5). This hypothesis is supported by previous studies demonstrating that obesity potentializes the inflammatory process of asthma, edema and airway smooth muscle contraction that can increase small airway collapse and airflow limitation, leading to dynamic hyperinflation (3).

Another important result of the present study is that asthmatic patients who lost $\geq 5\%$ of their body weight significantly delayed the onset of DH after the intervention. Although the total duration of the submaximal exercise test (T_{lim}) was not different between groups, patients who lost more weight were able to exercise longer without presenting DH. These findings could have positive effects on adherence to physical activity during daily life. Although the association is speculative, the delayed onset of DH and LFE could enable patients to perform more activities of daily living with fewer symptoms and limitations, which would improve their health-related quality of life. In support of our hypothesis, the group of patients who lost more weight presented improvements in the clinical control of asthma and in HRQoL. Interestingly, the areas of improvement noted on the AQLQ were the physical limitation and symptoms domains.

The results of the present study suggest that programs for obese individuals with asthma should prioritize weight loss $\geq 5\%$ because this change can reduce dynamic hyperinflation and airway inflammation as well as improve the quality of life. Although this weight loss is considered modest by the GINA's statement, it seems to reduce the physical limitation imposed by obesity and to avoid

an increase in the consumption of medication, which is considered a goal in asthma treatment (22). Weight loss is a very difficult task to achieve and requires the involvement of a multidisciplinary team as used in our study. Previous studies have suggested that a more pronounced weight loss ($\geq 7\%$) seems to have an important role in increasing physical activities of daily living (18). As a consequence, the results of our study confirm previous findings demonstrating that weight loss improves asthma control (12, 17) and has important repercussions in the improvement of respiratory mechanics during exercise, decreasing the symptoms of asthma and the degree of limitation in daily life activities.

Some limitations of the present study should be considered. Initially, most of the participants were female, which could reduce the external validity of our findings. However, the higher number of females in the studied population is supported by previous studies analyzing the obese asthmatic phenotype (10,12). Second, the cut-off of 5% weight loss was selected according to previous studies indicating that 5% was the cut-off for improvement in clinical control and lung function in obese patients with asthma (22, 49). Third, there is a lack of standardization in the reduction of inspiratory capacity that represents DH. We used a 10% reduction of the basal value as the cut-off because it is greater than the minimum variability accepted between maneuvers (39). Fourth, the expiratory flow limitation was evaluated by plotting flow-volume envelopes, which may have led to overestimation of the results (27,29); however, this method has been widely used in the literature (1,45,52) to evaluate and quantify expiratory flow limitation during exercise. Fifth, the inclusion of a control group with non-asthmatic obese individuals could have improved our understanding of the effect of weight loss on lung function in obese individuals. However, previous studies have already observed that a weight loss program in non-asthmatic obese subjects has a modest effect on respiratory mechanics, and this effect is related to the loss of fat in the chest wall (2, 4). Finally, it would also be important future studies evaluating the involvement of other variables related to body fat and

dynamic hyperinflation, such as the level of inflammatory mediators (leukotrienes and prostaglandins) (8).

In conclusion, moderate weight loss can improve dynamic hyperinflation in obese patients with asthma by decreasing abdominal fat. Moreover, a minimum 5% weight loss delays the onset of dynamic hyperinflation and induces a clinical improvement in asthma-related quality of life and clinical control. This is the first study to evaluate dynamic hyperinflation after a weight-loss program in obese patients with asthma, and further studies are required to confirm our hypotheses.

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DISCLOSURES

None of the authors have any conflicts of interest to report.

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FIGURE LEGENDS

Figure 1. Data are expressed as the mean change in the inspiratory capacity (IC) from baseline during submaximal exercise testing (75% of the maximal peak aerobic capacity ($\text{VO}_{2\text{peak}}$)). After the intervention, patients lost $\geq 5\%$ of their body weight (black closed dot) or $< 5\%$ of their body weight (gray open dot). Continuous line = before the intervention; dashed line = after the weight loss program. V_E = minute ventilation during exercise; L/min = liters per minute; DH = dynamic hyperinflation cut-off (49). Values are the mean $\pm$ SE. Comparisons were performed using a two-way repeated-measures analysis of variance (ANOVA). * $p < 0.05$ compared with baseline in the group that lost $\geq 5\%$ of the body weight.

Figure 2. The onset time of occurrence of DH (A) and EFL (B) post-intervention in patients who were hyperinflated ($\geq 5\%$ group, $n=15$; $< 5\%$ group, $n=20$). Data are represented as the median (10^{th} – 90^{th} percentiles). DH: dynamic hyperinflation; LFE: limitation of expiratory flow. Comparisons between groups were performed using two-way repeated-measures analysis of variance (ANOVA).

Figure 3. Linear correlations between the waist circumference variations and dynamic hyperinflation - inspiratory capacity (IC) variations in the $\geq 5\%$ group (black closed dot) and the $< 5\%$ group (gray open dot). Pearson's correlation test was used.

TABLE LEGENDS**Table 1.** Baseline characteristics of the study participants**Table 2.** Quality of life and asthma control data before and after intervention**Table 3.** Anthropometric and body composition data before and after intervention**Table 4.** Analysis of pulmonary function and muscle strength before and after weight loss**Table 5:** Analysis of airway and systemic inflammatory markers

641 Table 1

Variables	≥5% Group (n=19)	<5% Group (n=23)
Anthropometric		
Age, years	46.4 ± 7.7	48.2 ± 7.9
Weight, Kg	90.1 ± 9.7	92.5 ± 9.6
BMI, Kg/m ²	37.5 ± 2.8	38.2 ± 2.3
Fat mass, Kg	43.7 ± 6.2	44.7 ± 5.7
Fat free mass, Kg	45.7 ± 4.7	47.5 ± 7.0
Waist circumference, cm	111.1 ± 8.0	112.6 ± 5.5
Medication		
ICS dose, µcg/day	1007.9 ± 334.3	1156.5 ± 426.2
LABA dose, µcg/day	42.5 ± 41.9	29.5 ± 9.4
Pulmonary Function		
FEV ₁ , L	2.09 ± 0.50	1.99 ± 0.43
, %	80.8 ± 16.1	77.9 ± 13.1
FEV ₁ /FVC	0.7 ± 0.1	0.7 ± 0.1
ERV, L	0.47 ± 0.34	0.30 ± 0.24
, %	40.2 ± 26.9	30.1 ± 18.4
RV, L	2.12 ± 0.71	2.18 ± 0.55
, %	163.6 ± 45.1	170.1 ± 50.4
TLC, L	5.14 ± 0.80	5.09 ± 0.76
, %	116.5 ± 12.3	116.0 ± 19.1
RV/TLC	40.5 ± 9.2	42.7 ± 7.9
% of change in FEV ₁ post-BD	18.5 ± 6.62	24.9 ± 12.1
Asthma-related variables		
Onset asthma in childhood, n (%)	14 (73.7)	16 (69.6)
ACQ, score	2.0 ± 0.9	1.9 ± 0.7
Aerobic fitness		
Peak VO ₂ , mL O ₂ /Kg/min	15.9 ± 2.8	15.3 ± 1.7
, %	83.7 ± 11.3	81.9 ± 9.1
Comorbidities		
Obstructive sleep apnea, n (%)	2 (11)	3 (13)
Gastroesophageal reflux, n (%)	12 (63)	11 (48)
Hypertension, n (%)	7 (37)	11 (48)

Rhinitis, n (%)

17 (89)

18 (78)

Abbreviations: The data are presented as the mean±SD, or n (%). No differences between groups were observed at baseline ($P>0.05$). ICS = inhaled corticosteroids; LABA = long-acting β_2 -agonists; BMI: body mass index; FEV₁: forced expiratory volume in 1s; FVC: force vital capacity; ERV: expiratory reserve volume; RV: residual volume; TLC: total lung capacity; BD: bronchodilator; ACQ: asthma control questionnaire; Peak VO₂: peak oxygen consumption.

649 **Table 2**

Variables	≥5% Group (n=19)		<5% Group (n=23)		Group x time (p-value)
	Baseline	Change	Baseline	Change	
AQLQ domains					
Activity limitations, score	3.3 ± 0.9	1.2 ± 1.2*	3.4 ± 0.8	0.4 ± 1.0	0.02
Symptoms, score	3.6 ± 1.3	1.3 ± 1.5*	4.3 ± 0.9	0.3 ± 0.8	0.01
Emotional function, score	3.5 ± 1.6	1.5 ± 1.7*	3.2 ± 1.7	0.6 ± 1.5	0.08
Environmental stimuli, score	3.3 ± 1.5	1.2 ± 1.8*	2.7 ± 1.6	0.7 ± 1.6*	0.41
Total, score	3.4 ± 1.1	1.3 ± 1.3	3.6 ± 0.8	0.4 ± 0.8	0.01
Asthma control questionnaire					
ACQ7, score	2.0 ± 0.9	-0.7 ± 1.0*	1.9 ± 0.7	-0.4 ± 0.8*	0.35

650 **Abbreviations:** The data are presented as the mean±SD. AQLQ: asthma quality of life questionnaire; ACQ: asthma
651 control questionnaire. Significant effect group x time interaction in bold, two-way repeated-measures analysis of variance
652 (ANOVA). * p<0.05 vs. pre-intervention.
653

654 **Table 3**

Variables	≥5% Group (n=19)		<5% Group (n=23)		Group x time
	Baseline	Change	Baseline	Change	(p-value)
Body composition					
Weight, Kg	90.1 ± 9.66	-7.24 ± 2.63*	92.5 ± 9.64	-2.17 ± 1.92*	<0.001
BMI, Kg/m ²	37.5 ± 2.80	-2.98 ± 0.89*	38.2 ± 2.29	-0.90 ± 0.80*	<0.001
Waist circumference, cm	111.1 ± 7.99	-8.05 ± 5.30*	112.6 ± 5.49	-4.09 ± 4.79*	0.015
Fat mass, Kg	43.7 ± 6.23	-6.75 ± 3.15*	44.8 ± 5.66	-1.75 ± 2.26*	<0.001
Fat free mass, Kg	45.7 ± 4.71	-0.14 ± 1.46	47.5 ± 7.08	-0.47 ± 1.31	0.454
Body fat, %	48.5 ± 3.17	-4.74 ± 3.23*	48.6 ± 3.62	-1.92 ± 2.94*	<0.001
Trunk lean mass, Kg	21.9 ± 2.06	-0.23 ± 0.87	23.1 ± 3.25	-0.22 ± 0.91	0.974
Trunk fat mass, Kg	21.0 ± 2.60	-2.15 ± 1.24*	22.1 ± 2.52	-0.91 ± 0.98*	<0.001
Visceral fat area, cm ²	181.7 ± 26.2	-23.7 ± 12.5*	185.6 ± 20.2	-10.1 ± 13.9*	0.002

Abbreviations: Data are presented as mean±SD. BMI: body mass index. Significant effect group x time interaction in bold, two-way repeated-measures analysis of variance (ANOVA). * p<0.05 vs. pre-intervention.

Table 4

Variables	≥5% Group (n=19)		<5% Group (n=23)		Group x time (p-value)
	Baseline	Change	Baseline	Change	
Pulmonary function					
FEV ₁ , L	2.09 ± 0.50	0.03 ± 0.60	1.99 ± 0.43	0.04 ± 0.31	0.93
, %	80.8 ± 16.1	0.89 ± 8.66	77.9 ± 13.1	2.11 ± 13.3	0.73
FVC, L	2.99 ± 0.56	0.04 ± 0.21	2.81 ± 0.54	0.06 ± 0.36	0.76
, %	95.7 ± 11.0	0.81 ± 6.82	90.6 ± 15.0	2.59 ± 12.5	0.58
TLC, L	5.14 ± 0.80	0.02 ± 0.49	5.09 ± 0.76	-0.02 ± 0.45	0.77
, %	116.5 ± 12.3	0.20 ± 10.4	116.0 ± 19.1	-0.35 ± 10.2	0.86
ERV, L	0.47 ± 0.34	0.06 ± 0.30	0.30 ± 0.24	0.34 ± 0.21	0.62
, %	40.2 ± 26.9	7.37 ± 29.8	30.1 ± 18.4	3.30 ± 15.7	0.57
RV, L	2.12 ± 0.71	-0.01 ± 0.48	2.18 ± 0.55	0.05 ± 0.36	0.59
, %	163.6 ± 45.1	0.22 ± 36.2	170.1 ± 50.4	3.95 ± 28.4	0.71
FRC, L	2.59 ± 0.74	0.05 ± 0.35	2.55 ± 0.61	0.07 ± 0.42	0.86
, %	97.1 ± 24.6	2.07 ± 12.9	95.8 ± 23.7	2.68 ± 15.9	0.89
Quadriceps muscle function					
Muscle strength, Kg	34.5 ± 4.31	2.94 ± 5.12	33.4 ± 8.04	4.73 ± 6.17	0.36
Muscle endurance, repetitions	30.4 ± 11.8	2.11 ± 9.67	25.3 ± 10.2	3.61 ± 9.97	0.62

Abbreviations: The data are presented as the mean±SD or n (%). FEV₁: forced expiratory volume in 1s; ERV: expiratory reserve volume; RV: residual volume; TLC: total lung capacity; FRC: functional residual capacity; FVC: force vital capacity. Two-way repeated-measures analysis of variance (ANOVA) were used.

Table 5

Variables	≥5% Group (n=19)		<5% Group (n=23)		Group x time (p-value)
	Baseline	Change	Baseline	Change	
Airway inflammation					
Fe _{NO} , ppb	28.09 ± 17.71	-7.94 ± 12.24	22.28 ± 10.51	-1.19 ± 8.88	0.04
Interleukins					
IL-2 fg.mL ⁻¹	72.12 ± 95.54	-25.33 ± 72.55	44.52 ± 62.99	19.07 ± 45.92	0.02
IL-4, fg.mL ⁻¹	10.72 ± 17.41	-3.13 ± 7.72	8.62 ± 25.29	6.12 ± 19.09	0.05
IL-5, fg.mL ⁻¹	84.21 ± 101.76	-29.55 ± 99.04	40.64 ± 43.96	4.49 ± 45.60	0.14
IL-10, fg.mL ⁻¹	32.23 ± 26.17	41.83 ± 63.44	52.45 ± 69.92	-8.41 ± 37.45	0.003
Systemic markers					
Leptin, mg.L ⁻¹	19.10 ± 5.94	-1.57 ± 4.46	17.70 ± 6.88	0.04 ± 4.74	0.266
Adiponectin, mg.L ⁻¹	11.49 ± 8.32	2.58 ± 6.60	12.39 ± 7.49	-0.04 ± 4.20	0.126
VEGF, fg.mL ⁻¹	48.29 ± 18.81	14.24 ± 26.32	38.28 ± 39.04	-2.81 ± 23.15	0.031
CRP, mg.L ⁻¹	8.65 ± 5.43	-2.43 ± 6.50	8.65 ± 6.43	-0.77 ± 6.87	0.429
Vitamin D, ng.mL ⁻¹	20.00 ± 6.75	3.68 ± 7.27	27.87 ± 5.77	-1.17 ± 5.14	0.015

Abbreviations: Data are presented as the mean±SD. IL: interleukins; VEGF: vascular endothelial growth factor; CRP: C-reactive protein; FeNO: fractional exhaled nitric oxide. Significant effect group x time interaction in bold, two-way repeated-measures analysis of variance (ANOVA).

FIGURE 1

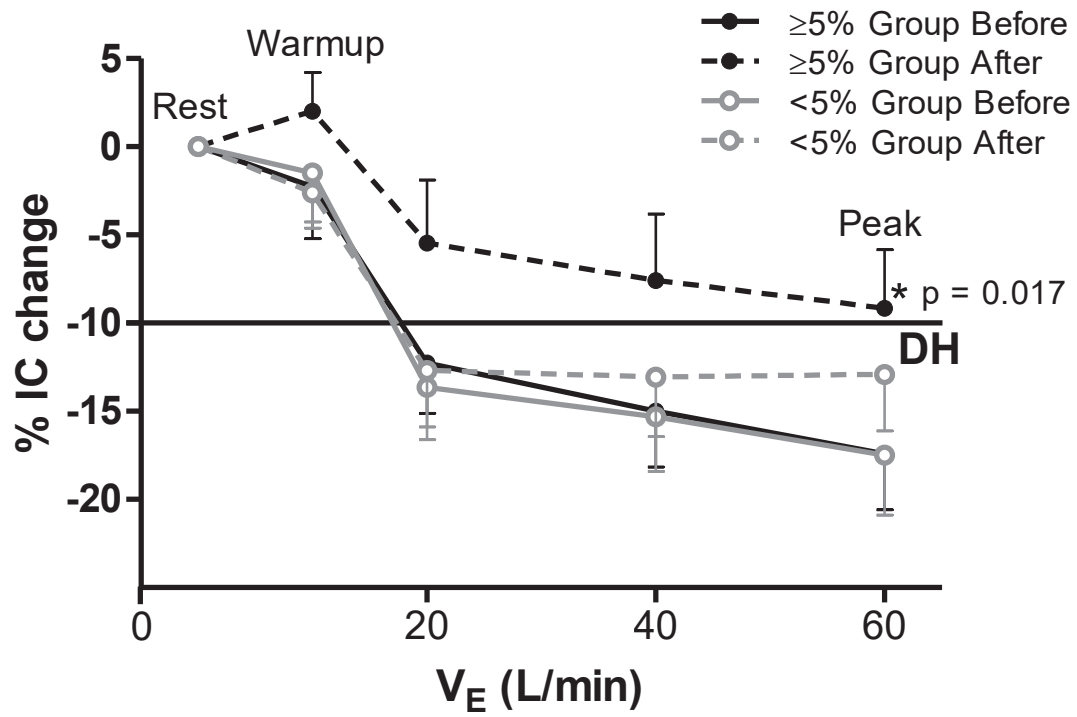


FIGURE 2

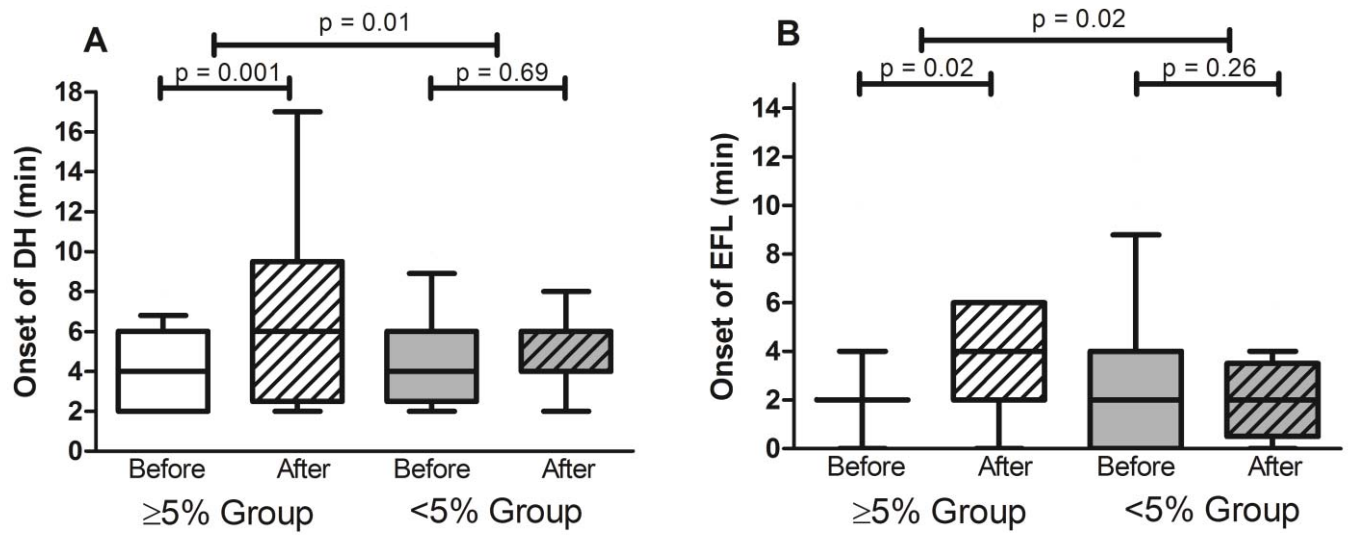


FIGURE 3

