ORIGINAL ARTICLE

The Role of Exercise in a Weight-Loss Program on Clinical Control in Obese Adults with Asthma

A Randomized Controlled Trial

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Abstract

Rationale: Clinical control is difficult to achieve in obese patients with asthma. Bariatric surgery has been recommended for weight loss and to improve asthma control; however, the benefits of nonsurgical interventions have been poorly investigated.

Objectives: To examine the effect of exercise training in a weight-loss program on asthma control, quality of life, inflammatory biomarkers, and lung function.

Methods: Fifty-five obese patients with asthma were randomly assigned to either a weight-loss program plus exercise (WL + E group, n = 28) or a weight-loss program plus sham (WL + S group, n = 27), where the weight-loss program included nutrition (caloric restriction) and psychological therapies. The WL + E group incorporated aerobic and resistance muscle training, whereas the WL + S group incorporated breathing and stretching exercises.

Measurements and Main Results: The primary outcome was clinical improvement in asthma control over 3 months. Secondary outcomes included quality of life, lung function, body composition, aerobic capacity, muscle strength, and inflammatory/antiinflammatory biomarkers. After 3 months, 51 patients were analyzed. Compared with the WL + S group, the WL + E group demonstrated improved clinical control scores (median [25th to 75th percentile], −0.7 [−1.3 to −0.3] vs. −0.3 [−0.9 to 0.4]; $P = 0.01$) and greater weight loss (mean ± SD, −6.8% ± 3.5 vs. −3.1% ± 2.6; $P < 0.001$) and aerobic capacity (median [25th to 75th percentile], 3.0 [2.4 to 4.0] vs. 0.9 [−0.3 to 1.3] ml $O_2 \times kg^{-1} \times min^{-1}$; $P < 0.001$). These improvements in the WL + E group were also accompanied by improvements in lung function, antiinflammatory biomarkers, and vitamin D levels, as well as reductions in airway and systemic inflammation.

Conclusions: Adding exercise to a short-term weight-loss program should be considered as a useful strategy for achieving clinical control of asthma in obese patients.

Clinical trial registered with www.clinicaltrials.gov (NCT 02188940).

Keywords: asthma; obesity; exercise training; clinical trial

In recent decades, epidemiologic studies have demonstrated an increased prevalence of asthma and obesity, suggesting an association between the two conditions (1–3). According to current guidelines, clinical control is difficult to achieve in obese patients because of mechanical factors, distinct types of inflammation, comorbidities, and other undefined factors (4). This highlights the need for strategies to reduce weight as a way to improve the management of asthma in obese patients.

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At a Glance Commentary

Scientific Knowledge on the Subject: Clinical control is difficult to achieve in obese patients with asthma, and interventions for weight loss have been investigated to improve the control of asthma in these patients. However, the role of exercise in nonsurgical interventions to improve clinical control remains poorly investigated.

What This Study Adds to the Field: This randomized controlled trial with a blind assessment provides the first evidence that exercise training improves body composition and physical fitness and has an additional effect in modulating the inflammatory/antiinflammatory balance, contributing to improvement in asthma control and health-related quality of life in obese adults with asthma.

Nonrandomized controlled trials using bariatric surgery in obese patients with asthma (body mass index [BMI] >40 or >35 kg/m^2 with comorbidities) have suggested positive effects on asthma outcomes, such as a reduction in symptoms and airway hyperresponsiveness (5–7). However, surgical interventions do not always lead to a direct lifestyle change, which is the first-line therapy for weight loss (8), and surgery is not indicated for most obese patients with asthma. A Cochrane review (9) evaluating nonsurgical weight-loss interventions for obese patients with asthma found that only one of four randomized controlled trials (RCTs) reviewed included exercise training (10). This one RCT showed that caloric restriction induced modest weight reductions and improved asthma control. Nevertheless, exercise training either alone or in combination with diet did not add significant benefits to asthma control (10). Two other studies (11, 12) investigated the effects of behavioral weight-loss interventions, which included a counseling program to increase physical activity levels instead of an exercise training program. Ma and coworkers (11) did not observe an effect of a weight-loss program on any clinical asthma outcomes. In contrast, Pakhale and coworkers (12), in a nonrandomized study, observed a benefit of a weight-loss program on asthma control, lung function, and weight loss.

Even with the findings of these studies, little is known about the effects of an exercise training program on obese patients with asthma. Conversely, exercise training as an add-on therapy in nonobese patients with asthma has been shown to improve quality of life and asthma symptoms (13), and reduce airway inflammation (14) and corticosteroid consumption (15). In addition, studies on animal models of asthma have demonstrated that exercise training reduces airway responsiveness and inflammation by reducing levels of T-helper cell type 2 IL-4, IL-5, IL-13 (16–18), and chemokine (C-C motif) ligand 2 (CCL2) (18), and increasing levels of IL-10, an antiinflammatory cytokine (17). Recently, these results were partially confirmed by an RCT in nonobese patients with asthma, in which aerobic training reduced bronchial hyperresponsiveness and serum levels of the proinflammatory cytokine IL-6 and chemokine CCL2 (19).

Because exercise is an effective intervention for patients with asthma (13–15) and obese individuals (20–22), we hypothesized that exercise performed at a proper intensity level would improve aerobic capacity and increase weight loss in obese patients with asthma, leading to improvements in their asthma control and quality of life. Airway and systemic chronic inflammation and lung function were also evaluated to better understand how exercise and weight loss influence asthma control. Some of the results of this study have been previously reported in the form of an abstract (23).

Methods

Subjects

We recruited outpatients with moderate/severe asthma and a BMI greater than or equal to 35 and less than 40 kg/m^2, who were under optimal medical treatment, clinically stable, physically inactive, and between 30 and 60 years old. All participants signed the written informed consent approved by the Hospital Ethics Committee. Exclusion criteria included cardiovascular, musculoskeletal, or other chronic pulmonary diseases; uncontrolled hypertension or diabetes; weight changes greater than 5% and/or antiobesity drug use within 6 months; bariatric surgery; smokers/ex-smokers; and pregnancy. Detailed methods are presented in the online supplement and as previously reported (24).

Experimental Design

This RCT involved two arms and blinded outcome assessments performed before and after treatment. Asthma pharmacotherapy was maintained during follow-up. All eligible patients received a 6-hour educational program and were randomly assigned (computer-generated) with concealed allocation into either a weight-loss program with sham exercise (WL + S group) or the same program but with aerobic and resistance exercise (WL + E group). The long-term effect (6 and 12 mo after randomization) was evaluated by obtaining body weight from patients' medical records.

Treatment Arms

WL + S group. The weight-loss program was conducted by a nutritionist and psychologist during 12 individual hypocaloric diet counseling sessions (25) and was supported by behavioral techniques (26). Sham exercises (stretching and breathing) did not affect asthma control (two sessions per week, 3 mo) (13, 14).

WL + E group. The WL + E group incorporated aerobic and resistance exercises (two sessions per week, 3 mo) into the weight-loss program. Aerobic training intensities were based on 50–75% of peak $\dot{V}O_2$ (27). Patients performed resistance training for major muscle groups, used an accelerometer, and completed a physical activity diary.

Outcome Assessments

The primary outcome was clinical improvement in Asthma Control Questionnaire (ACQ) scores, a validated tool with seven questions related to asthma symptoms, rescue medication, and lung function (28). Asthma exacerbation was defined as previously described (19). Asthma-related quality of life was assessed using the Asthma Quality of Life Questionnaire (AQLQ) (29, 30). Aerobic capacity was evaluated using a cardiopulmonary exercise test (31), levels of daily life physical activity were quantified using an accelerometer (GT3X; Actigraph, Pensacola, FL) and peripheral muscle strength via a one-repetition-maximum

resistance test (32). Spirometry and lung volume measurements were quantified via whole-body plethysmography (33, 34). Anthropometric measurements and body composition were evaluated using a standardized protocol (35–37) and an octopolar bioelectrical impedance analysis (38).

Airway inflammation was quantified using the exhaled fraction of nitric oxide (F_{ENO}) (39). Serum levels of IL-1, IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, tumor necrosis factor (TNF)-α, vascular endothelial growth factor, transforming growth factor-β, and the chemokines CXCL9, CXCL10, CXCL8, CCL2, and CCL5 were analyzed using a cytometric bead array. Serum leptin and adiponectin were analyzed via ELISA, C-reactive protein via turbidimetry, and cortisol and 25-hydroxy-vitamin D [25(OH)D] via chemiluminescence assay.

Data Analysis

A sample size of 46 subjects was estimated based on the ACQ (40, 41). Treatment-by-time interactions were analyzed via a two-way repeated-measures analysis of variance and categorical outcomes via a chi-square test. Holm-Sidak corrections were applied to adjust for multiple comparisons. Linear correlations were used to test the associations among changes in weight, aerobic fitness, and clinical asthma outcomes, and a multiple regression to identify factors predictive of clinical control. All analyses were conducted with intention-to-treat using Sigma Stat 3.5 (Chicago, IL).

Results

Baseline Characteristics

A total of 645 subjects were assessed for eligibility, 590 were excluded, and 55 were randomized into two groups (Figure 1). Four participants (two in each group) were lost during follow-up. As a result, 51 participants were included in the analysis with intention-to-treat (25 WL + S and 26 WL + E). Both groups had similar baseline characteristics (Table 1). Participants were mostly female, with moderate obesity (mean [SD] BMI, 37.8 [2.5] kg/m^2) and low aerobic fitness (peak $\dot{V}O_2$, 15.5 [2.5] ml $O_2 \times kg^{-1} \times min^{-1}$). All patients were under inhaled corticosteroid treatment and long-acting β_2 bronchodilators. Mean ACQ scores were 2.0 (0.8), and 37 patients were classified as having uncontrolled asthma (ACQ >1.5; 68% in WL + E and 76% in WL + S).

Weight Loss, Aerobic Capacity, and Muscle Strength

After 3 months of the intervention, the WL + E group showed a greater reduction in body weight than the WL + S group (−6.8% [3.5%] vs. −3.1% [2.6%] of body weight, respectively; $P < 0.001$) (Figure 2A). Subjects in the WL + E group had a greater reduction in BMI and waist circumference than subjects in the WL + S group (−2.6 ± 1.3 vs. −1.0 ± 1.1 kg/m^2 and −7.5 ± 4.9 vs. −3.3 ± 4.2 cm, respectively). Total fat mass and visceral fat mass were decreased after both interventions, but the reduction was greater in the WL + E group than in the WL + S group ($P < 0.001$) (Figures 2B and 2D), whereas lean mass decreased in the WL + S

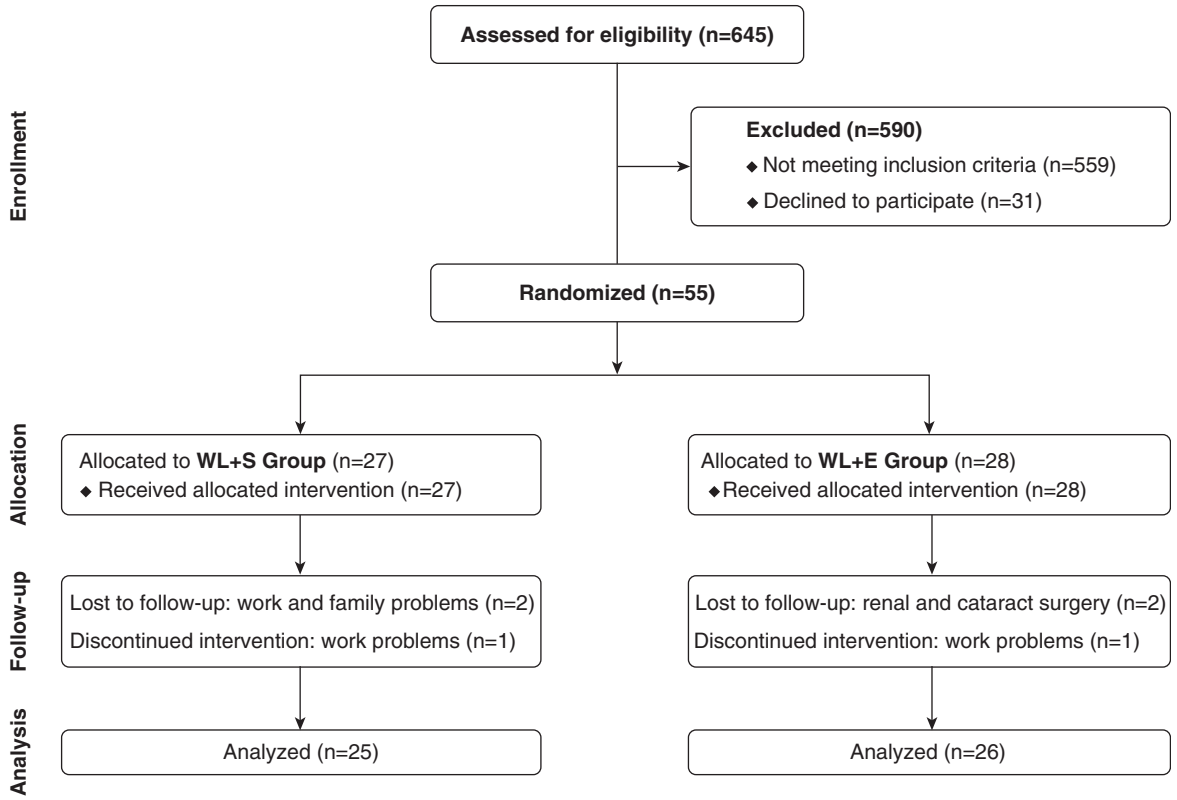

Figure 1. CONSORT diagram of the study participants. WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.

Table 1. Baseline Characteristics of the Study Participants

Characteristic	WL + S Group (*n* = 25)	WL + E Group (*n* = 26)
Anthropometric data		
Female sex	25 (100)	25 (96)
Age, yr	48.5 ± 9.6	45.9 ± 7.7
Weight, kg	89.5 ± 9.5	91.7 ± 9.9
BMI, kg/m^2	37.2 ± 2.1	38.1 ± 2.8
Medication		
ICS dose, μg/d	1,184 ± 492.2	1,051 ± 337.1
LABA dose, μg/d	36.7 ± 34.9	40.3 ± 36.1
Pulmonary function		
FEV_1, %	75.7 ± 17.4	80.9 ± 15.3
FEV_1/FVC, %	70.2 ± 10.1	69.6 ± 9.9
ERV, %	32.2 ± 15.7	34.7 ± 22.9
RV, %	168.2 ± 54.6	162.7 ± 40.6
% change FEV_1 post-BD	22.4 ± 12.6	21.6 ± 8.4
Asthma-related variables		
Onset of asthma in childhood	15 (60)	15 (57.7)
ACQ score	2.1 ± 0.7	2.0 ± 0.9
Blood eosinophils, cells/mm^3	353.3 ± 239.1	384.0 ± 206.6
Aerobic fitness		
Peak $\dot{V}O_2$, ml $O_2 \times kg^{-1} \times min^{-1}$	15.0 ± 2.6	16.0 ± 2.4
Comorbidities		
Obstructive sleep apnea	2 (8)	3 (11)
Gastroesophageal reflux	13 (52)	14 (54)
Hypertension	12 (48)	10 (39)
Rhinitis	19 (76)	20 (77)

Definition of abbreviations: ACQ = Asthma Control Questionnaire; BD = bronchodilator; BMI = body mass index; ERV = expiratory reserve volume; ICS = inhaled corticosteroids; LABA = long-acting β_2-agonists; RV = residual volume; WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.
The data are presented as the means ± SD or n (%). No differences between treatment arms were observed at baseline ($P > 0.05$).

group but remained the same or was slightly increased in the exercise group (Figure 2C). Patients from both groups maintained their weight loss after 6 months; however, the regaining of body weight was observed in the WL + S group after 1 year (*see* Figure E1 in the online supplement). Patients in the WL + E group exhibited an increase in peak $\dot{V}O_2$ (Figure 2E), in muscle strength (Figure 2F, Table 2) ($P < 0.001$), and in the daily life physical activity levels (3,274 ± 2,693 vs. 729 ± 1,145 steps/day; $P < 0.001$) compared with the effects in the WL + S group.

Effects on Clinical Control of Asthma

The ACQ scores in the WL + E group improved from 2.0 (1.4–2.7) at baseline to 1.1 (0.4–1.5) at 3 months ($P < 0.001$), whereas the ACQ scores did not change in the WL + S group (Figure 3A). After the interventions, a clinically significant improvement in asthma control, as defined by a change in ACQ scores of greater than 0.5 points, was found in 69% of patients in the WL + E group and in 36% in the WL + S group ($P = 0.03$) (Figure 3B). The proportions of patients who experienced no exacerbations during follow-up were 53% in the WL + E group and 20% in the WL + S group ($P = 0.03$).

Regardless of the treatment group, changes in ACQ scores were linearly correlated with improvements in aerobic capacity ($r = -0.59$) and weight loss ($r = -0.54$) ($P < 0.001$) (Figure 4). A linear multiple regression analysis demonstrated that weight loss and aerobic capacity were independent factors accounting for 42% of the change in ACQ scores when the following dependent variables were taken into account: weight loss, peak $\dot{V}O_2$, FVC, F_{ENO}, IL-10, and adiponectin.

$$\left[\Delta \text{ ACQ score} = 0.08 + (0.07 \times \% \text{ weight loss}) - \left(0.15 \times \Delta \text{ peak } \dot{V}O_2\right)\right];$$

$P = 0.01$ and $P < 0.003$ for weight loss and Δ peak $\dot{V}o_2$, respectively. *(1)*

Based on this equation, an increase of 2.8 ml $O_2 \times kg^{-1} \times min^{-1}$ in peak $\dot{V}O_2$ or a decrease in weight of 6.0 kg promotes improvements in asthma control.

Asthma-Specific Quality of Life

For the AQLQ, treatment-by-time interactions were observed in relation to the activity limitation ($P < 0.01$) domain and in the total score, with better results observed in the WL + E group ($P = 0.03$) (Figure 3C, Table 2). In addition, a within-group improvement was observed in the other three domains in the WL + E group ($P < 0.01$) but only in the environmental stimuli domain in the WL + S group ($P < 0.05$); however, there were no differences between the groups ($P > 0.05$) (Table 2) in these domains. The proportion of patients who had a clinically significant improvement in their asthma-specific quality of life (change in total AQLQ score >0.5 points) was 65% in the WL + E group and 40% in the WL + S group ($P = 0.12$) (Figure 3D).

Lung Function

FEV_1, FVC, and expiratory reserve volume significantly improved during follow-up in the WL + E group, but no change was observed in the WL + S group (Table 2). In addition, the interaction between group and time showed a significant improvement in the WL + E group for expiratory reserve volume (Table 2). No changes were observed in the FEV_1/FVC ratio or in the other pulmonary parameters in either group ($P > 0.05$) (*see* Table E1).

Airway and Systemic Inflammatory Changes

Before intervention, patients from both groups had an average F_{ENO} of 26.1 (14.5) ppb, and 45% of the patients (13 in the WL + E group, 10 in the WL + S group) had F_{ENO} levels higher than 25 ppb. After the intervention, only the WL + E group exhibited a decrease in F_{ENO} levels (Table 3) ($P < 0.001$). Among patients with levels of F_{ENO} greater than 25 ppb, there was an improvement in 75% of subjects in the WL + E group and 10% of subjects in the WL + S group ($P = 0.004$).

Regarding inflammatory and antiinflammatory biomarkers, the WL + E group showed a significant reduction in blood levels of CCL2, IL-4, IL-6, TNF-α, and leptin; increased levels of 25(OH)D, the anti-inflammatory marker IL-10, and serum adiponectin ($P < 0.05$); and an

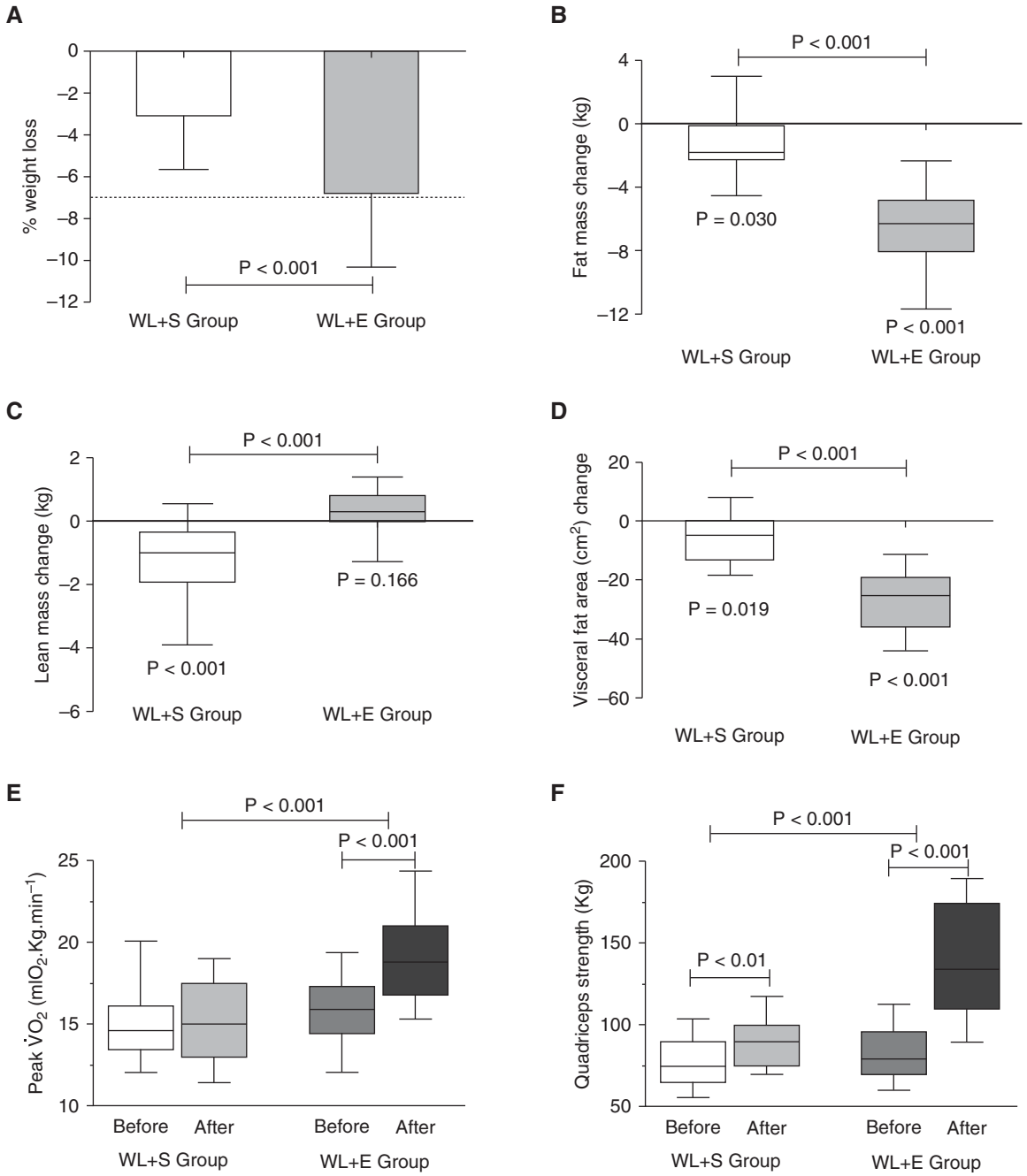

Figure 2. Changes over time in the percentage of weight loss (*A*), fat mass (*B*), lean mass (*C*), visceral fat area (*D*), aerobic capacity (*E*), and muscle strength (*F*). The data are presented as the means (SD), unpaired Student's *t* test (*A*), or medians (25th–75th percentiles), analysis of variance (*B–F*). WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.

improvement in the leptin/adiponectin ratio compared with the values in the WL + S group (Table 3). The CXCL9 and CXCL10 levels decreased significantly within the WL + E group after 3 months, but the difference between the groups was not significant ($P > 0.05$) (Table 3). IL-5, CXCL8, vascular endothelial growth factor, transforming growth factor-β, and cortisol levels did not change ($P > 0.05$) (*see* Table E1), and IL-1β, IL-2, IL-12, IL-13, and CCL5 levels were undetectable in the samples.

Possible Mechanisms

The improvement in the clinical control of asthma (ACQ scores) in the WL + S group was only linearly associated with a reduction in fat mass ($r = 0.60$; $P = 0.01$). In the WL + E group, the improvement in the ACQ scores was associated with a reduction in fat mass ($r = 0.50$; $P = 0.01$) and inflammatory biomarkers (IL-6: $r = 0.37$; $P = 0.05$; and Fe_{NO}: $r = 0.48$; $P = 0.01$) and with an increase in lung function (FVC: $r = -0.51$; $P < 0.01$), lean mass ($r = -0.45$; $P = 0.01$), aerobic fitness

Table 2. Group Comparisons of Anthropometric Data, Strength of Muscle Groups, Lung Function, and Quality of Life Domains during Follow-up

	WL + S Group (*n* = 25)		WL + E Group (*n* = 26)		Group × Time (*P* Value)
	Baseline	Change	Baseline	Change	
Anthropometric data variables					
Weight, kg	88.6 (84.4 to 94.4)	−2.9 (−3.9 to −1.4)*	91.1 (86.3 to 99.8)	−6.1 (−7.4 to −4.2)*	**<0.001**
BMI, kg/m^2	37.4 (35.2 to 38.7)	−1.1 (−1.8 to −0.4)*	37.7 (35.4 to 40.1)	−2.7 (−3.3 to −1.8)*	**<0.001**
Waist circumference, cm	112 (106.1 to 117.2)	−4.0 (−6.0 to −0.9)*	111 (106.0 to 118.0)	−6.2 (−11.0 to −3.0)*	**0.002**
Aerobic capacity					
$\dot{V}O_2$, ml/min	1,291 (1,178 to 1,475)	8.4 (−95.4 to 75.6)	1,423 (1,321 to 1,591)	156 (91.4 to 229.3)*	**<0.001**
Work rate, W	85.0 (69.0 to 98.7)	12.0 (−2.2 to 20.5)†	91.5 (83.0 to 103.0)	26.0 (22.0 to 39.0)*	**<0.001**
Strength of muscle groups, kg					
Calf muscles	70.0 (53.7 to 82.5)	10.0 (0.0 to 25.0)†	70.0 (60.0 to 90.0)	40.0 (30.0 to 70.0)*	**<0.001**
Pectoral muscles	4.0 (4.0 to 5.0)	1.0 (0.0 to 1.0)‡	5.0 (4.0 to 6.0)	2.0 (1.0 to 4.0)*	**<0.001**
Deltoid muscles	5.0 (4.0 to 6.0)	0.0 (0.0 to 2.0) ‡	5.0 (5.0 to 6.0)	3.0 (2.0 to 4.0)*	**<0.001**
Lung function, L					
FEV_1	1.8 (1.6 to 2.1)	0.06 (−0.1 to 0.1)	2.1 (1.8 to 2.6)	0.05 (−0.1 to 0.3)‡	0.364
FVC	2.7 (2.4 to 3.1)	0.0 (−0.2 to 0.3)	2.8 (2.6 to 3.3)	0.2 (−0.1 to 0.4)†	0.078
TLC	5.1 (4.4 to 5.4)	0.1 (−0.2 to 0.3)	5.0 (4.5 to 5.4)	0.2 (−0.3 to 0.5)	0.137
ERV	0.3 (0.2 to 0.5)	0.0 (0.06 to 0.08)	0.3 (0.2 to 0.5)	0.2 (−0.03 to 0.3)*	**0.038**
Quality of life domains (AQLQ)					
Activity limitation	3.2 (3.0 to 3.8)	0.2 (−0.1 to 0.8)	3.6 (2.7 to 3.9)	0.7 (0.2 to 2.0)*	**0.007**
Symptoms	4.1 (3.5 to 4.4)	0.4 (−0.1 to 0.8)	3.9 (3.4 to 4.9)	0.9 (0.2 to 1.4)*	0.084
Emotional function	3.4 (2.1 to 4.6)	0.6 (−0.3 to 1.9)	3.7 (1.8 to 4.6)	1.3 (0.2 to 2.6)*	0.125
Environmental stimuli	2.0 (1.4 to 3.5)	0.2 (−0.1 to 2.4)‡	3.5 (2.5 to 4.2)	1.1 (0.0 to 2.2)†	0.903

Definition of abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BMI = body mass index; ERV = expiratory reserve volume; TLC = total lung capacity; WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.
The data are presented as the medians (25th–75th). Significant effects of the group × time interaction according to analysis of variance are highlighted in bold.
*$P \leq 0.001$ versus preintervention.
†$P \leq 0.01$ versus preintervention.
‡$P < 0.05$ versus preintervention.

($\dot{V}O_2$: $r = -0.66$; $P < 0.001$), and antiinflammatory biomarkers (IL-10: $r = -0.44$; $P = 0.02$; and adiponectin: $r = -0.62$; $P = 0.02$) (Table 4). Among subjects who exercised, there was also an association between a reduction in fat mass and improvements in lung function (FVC: $r = 0.64$; $P < 0.001$) and inflammatory markers (IL-6: $r = 0.53$; $P = 0.04$; and F_{ENO}: $r = 0.54$, $P < 0.01$). Furthermore, there was an association between reduced inflammatory markers and increases in peak $\dot{V}O_2$ and lean mass (IL-6: $r = -0.40$; $P = 0.01$ and $r = -0.56$; $P < 0.01$; and F_{ENO}: $r = -0.41$; $P = 0.04$ and $r = -0.71$; $P < 0.001$, respectively) and between increased antiinflammatory biomarkers and increased peak $\dot{V}O_2$ and lean mass (IL-10: $r = 0.43$; $P = 0.03$ and 0.56; $P < 0.01$, respectively). An increase in $\dot{V}O_2$ was also associated with adiponectin levels ($r = 0.62$; $P < 0.001$) (Figure 5).

Discussion

This RCT with a blind assessment conducted on obese patients with asthma demonstrates that exercise training associated with a weight-loss program leads to greater weight loss and improvements in aerobic capacity and strength, resulting in better clinical control of asthma and an improved health-related quality of life compared with the results in patients who underwent the same weight-loss program without exercise training. These improvements in patients who exercised were also accompanied by ameliorations in lung function, antiinflammatory biomarkers, and vitamin D levels, as well as a reduction in inflammatory mediators. These results support the notion that weight reduction is important for the management of asthma in obese adults (9, 42) and demonstrate that exercise has additional antiinflammatory effects that contribute to improved asthma control in these patients.

In the present study, patients who incorporated exercise with dietary/psychological support experienced a 7% reduction in body weight and clinically improved their asthma control after 3 months of using first-line weight-loss therapy. Previous studies (10, 42) have also demonstrated clinical improvements in asthma following a weight-loss program. Patients in the study by Dias-Júnior and coworkers (42) lost approximately 10% of their body weight after 6 months by using antiobesity drugs, whereas Scott and coworkers (10) reported that patients had an approximately 8.5% reduction in body weight using meal replacements, such as shakes or liquids. These findings are particularly relevant because losing weight is undoubtedly difficult. However, our results are important because combining exercise with a diet program allows patients

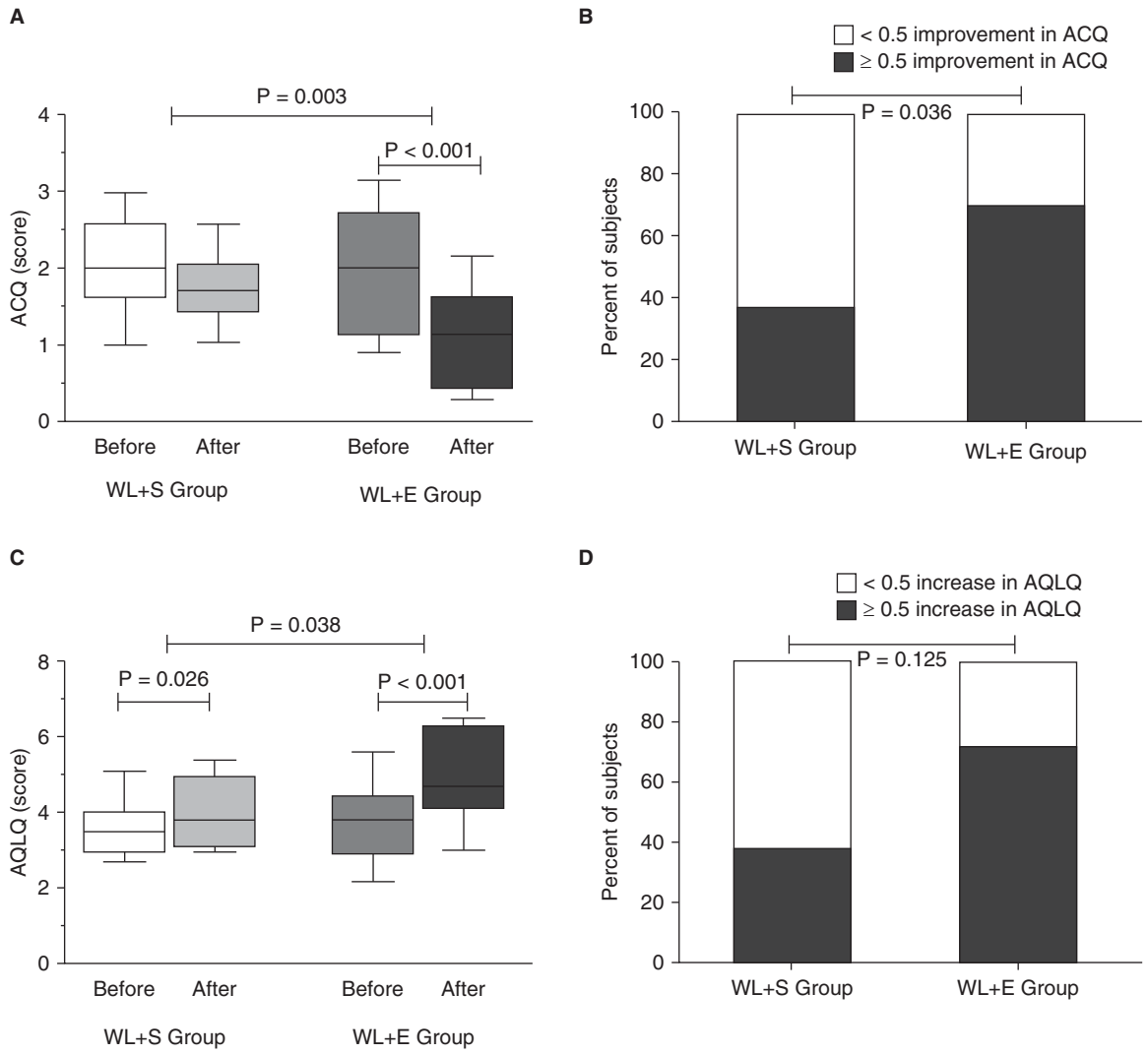

Figure 3. Changes over time in the clinical control of asthma (*A*) and quality of life (*C*). The data are presented as the medians (25th–75th percentiles), analysis of variance (*A* and *C*), or as %, chi-square test (*B* and *D*). ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire; WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.

to achieve better asthma control in a shorter period of time (3 mo) and with lower percent reductions in body weight (7%) than previously described (*see* Equation 1, Results) (10, 42).

For instance, based on Equation 1, two patients (one from each group) presented the same weight loss (6.6% of body weight), but only one of them (in the WL + E group) improved the peak $\dot{V}O_2$ (2.9 ml O_2/kg/min) and reached a clinical improvement in the ACQ (0.8 score). These results reinforce the fact that the reduction in body weight and the improvement in peak $\dot{V}O_2$ have independent and complementary effects on clinical control. According to the multivariate analysis we performed, the improvement in clinical control could be reached using only a dietary restriction; however, it would be necessary to have a more effective strategy or a longer period of intervention to achieve the same improvement on clinical control. Finally, the fact that our patients have lost weight in a short period with exercise training may have stimulated them to maintain their body weight for a long period as can be seen in Figure E1. These results are reinforced by the results of Dias-Junior and coworkers (42) that showed that a weight-loss program associating a low caloric intake with oral anorexiants induced a clinical improvement; however, it took a longer period (6 mo). Interestingly, the same study also showed that patients did not experience reduction in inflammation (Fe_{NO} and sputum-related indicators of inflammation) after the weight loss program without exercise training. Additionally, Scott and coworkers (10) observed that after 3 months, only the patients who performed exercise presented a reduction in airway inflammation. Finally, the fact that our patients have lost weight in a short period with exercise may have stimulated them to maintain the weight loss for a longer period (*see* Figure E1).

The mechanisms leading to improvements in asthma control in some patients who underwent psychological and nutritional intervention were very different from those observed when aerobic exercise was included in the intervention. A reduction in fat mass was the likely

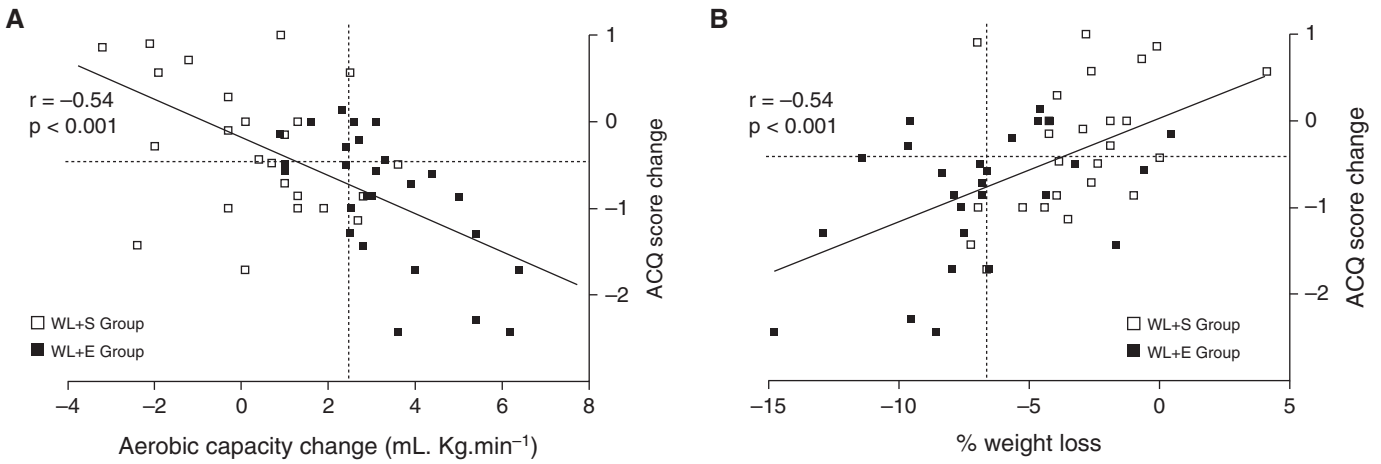

Figure 4. Correlations between changes in ACQ scores and changes in aerobic capacity (*A*) and the percentage of weight loss (*B*) during follow-up. Pearson correlation. ACQ = Asthma Control Questionnaire; WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.

mechanism that contributed to the improvement in clinical control observed in the group that did not perform exercise. When the weight loss was associated with exercise, however, a greater reduction in fat mass may have contributed to the improved clinical control by improving lung function and reducing levels of inflammatory biomarkers. Exercise also improved aerobic fitness ($\dot{V}O_2$) and muscle strength, which also led to a slight increased lean mass (muscle mass). Both mechanisms seem to contribute to improved clinical control by reducing the expression of inflammatory mediators (IL-6 and F_{ENO}) and increasing the expression of the antiinflammatory mediator IL-10 and serum adiponectin (Figure 5). Taken together, exercise intervention may have contributed to improved clinical control by increasing the reduction in fat mass, inducing other changes in body composition, and modulating airway and systemic inflammation.

Contrary to the results obtained by Scott and coworkers (10), we found that exercise associated with diet conferred a significant benefit on asthma control. The differences between these results can be attributed to several factors. In our study, we included patients with grade II obesity who had moderate and severe asthma, whereas Scott and coworkers (10) included

Table 3. Group Comparison for Airway and Systemic Inflammatory Markers

Variables	WL + S Group (*n* = 25)		WL + E Group (*n* = 26)		Group × Time (*P* Value)
	Baseline	Change	Baseline	Change	
Airway inflammation					
F_{ENO}, ppb	22.3 (16.2 to 32.6)	−0.2 (3.9 to 1.6)	24.7 (15.3 to 33.7)	−6.8 (-14.6 to 0.7)*	**<0.001**
Chemokines/IL					
CCL2, pg/ml	31.2 (18.3 to 50.9)	−2.2 (−4.1 to 2.1)	37.3 (19.8 to 43.7)	−4.4 (−11.8 to 1.8)†	**0.024**
CXCL9, pg/ml	33.0 (22.6 to 49.8)	−8.6 (−17.8 to 3.7)	32.0 (15.9 to 100.1)	−14.7 (−45.0 to 7.3)†	0.082
CXCL10, pg/ml	13.8 (6.2 to 23.0	−2.1 (−13.3 to 4.1)	12.9 (5.5 to 24.2)	−5.2 (−17.4 to 1.4)‡	0.267
IL-4, fg/ml	0.3 (0.0 to 7.1)	0.0 (−1.3 to 11.7)‡	4.9 (0.0 to 10.3)	0.0 (−4.8 to 0.7)	**0.004**
IL-6, fg/ml	1,842 (1,494 to 2,829)	49.9 (−368.5 to 927.5)	2,095 (1,583 to 3,081)	−490.1 (−848.8 to 82.9)†	**0.008**
IL-10, fg/ml	27.9 (13.4 to 57.8)	−2.4 (−20.7 to 7.9)	28.3 (5.4 to 51.6)	16.1 (1.3 to 47.8)*	**0.003**
Systemic markers					
Leptin, mg/L	15.2 (11.9 to 20.8)	1.2 (−1.0 to 2.9)	18.9 (14.0 to 22.0)	−1.8 (−5.5 to 1.6) †	**0.003**
Adiponectin, mg/L	10.0 (5.9 to 18.4)	−0.4 (−2.0 to 1.0)	9.0 (7.5 to 14.7)	1.1 (−1.7 to 7.6)†	**0.027**
Leptin/adiponectin	1.4 (0.8 to 2.8)	0.06 (−0.2 to 0.4)	1.7 (1.1 to 2.9)	−0.6 (−1.4 to 0.1)†	**0.009**
TNF-α, fg/ml	9.1 (0.0 to 28.2)	0.0 (−16.2 to 12.8)	38.5 (0.0 to 77.0)	−22.1 (−47.9 to 0.0)*	**0.018**
CRP, mg/L	6.7 (4.2 to 11.5)	−0.7 (−4.4 to 1.9)	7.0 (3.1 to 10.1)	−1.5 (−3.9 to 0.3)	0.295
Vitamin D, ng/ml	22.0 (18.0 to 24.2)	−1.0 (−3.2 to 2.0)	19.5 (17.0 to 22.0)	2.5 (−3.0 to 11.0)†	**0.012**

Definition of abbreviations: CCL2 = chemokine (C-C motif) ligand 2; CRP = C-reactive protein; CXCL9 = chemokine (C-X-C motif) ligand 9; CXCL10 = chemokine (C-X-C motif) ligand 10; F_{ENO} = fractional exhaled nitric oxide; TNF-α = tumor necrosis factor-α; WL + E = weight-loss program aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.

The data are presented as the medians (25th–75th). Significant effects of the group × time interaction are highlighted in bold, analysis of variance.

*$P \leq 0.001$ versus preintervention.

†$P \leq 0.01$ versus preinterventon.

‡$P < 0.05$ versus preintervention.

Table 4. Linear Correlation between Changes in Clinical Asthma Control and Changes in Body Composition, Aerobic Fitness, Lung Function, and Systemic Inflammatory Markers

	ACQ (WL + S Group)	ACQ (WL + E Group)
Body composition, kg		
Fat mass	0.60*	0.50*
Lean mass	0.10	−0.45*
Aerobic fitness		
Peak $\dot{V}o_2$, ml $O_2 \times kg^{-1} \times min^{-1}$	−0.33	−0.66*
Lung function		
FVC, L	−0.28	−0.51*
Proinflammatory and antiinflammatory biomarkers		
IL-6, fg/ml	−0.19	0.37*
F_{ENO}, ppb	0.02	0.48*
IL-10, fg/ml	0.27	−0.44*
Adiponectin, mg/L	0.26	−0.62*

Definition of abbreviations: ACQ = Asthma Control Questionnaire; F_{ENO} = fractional exhaled nitric oxide; WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.
Change in ACQ was used as the dependent variable, and the other variables were used as independent variables. Pearson correlation tests were used.
*$P < 0.05$.

overweight and obese patients with a wide range of asthma severity. Furthermore, half of their study population had intermittent or mild asthma. The inclusion of patients with mild asthma may explain why patients were considered physically active at baseline (10,000 steps/day) in the study by Scott and coworkers (10), whereas our patients with moderate and severe asthma were sedentary (approximately 7,000 steps/day) (43) and had a reduced aerobic capacity (approximately 15 ml O_2/kg/min). Thus, patients with more severe asthma may benefit more from exercise training, which is consistent with findings reported for nonobese individuals with asthma (19, 42, 44).

Another reason for the difference between these studies is the efficacy of the interventions used. The present study showed more weight loss caused by exercise, whereas Scott and coworkers (10) reported more weight loss caused by dietary restrictions. An additional relevant issue is the intensity of exercise performed during the intervention, which is important for achieving enhanced benefits (27). In our study, exercise intensity was based on cardiopulmonary exercise testing, similar to the approach of previous studies (14, 15, 19), whereas exercise intensity was not based on this information in the study by Scott and coworkers (10).

Our data also demonstrate that increased physical fitness augments weight loss and reduces the levels of F_{ENO} and the serum proinflammatory mediators IL-4, IL-6, TNF-α, CCL2, and leptin and increased the levels of IL-10 and serum adiponectin. This antiinflammatory effect is supported by previous studies on experimental animal models of asthma, which have demonstrated that exercise training increases IL-10 levels (18) and reduces T-helper type 2 cytokines (IL-4, IL-5, and IL-13) (16–18, 45) and chemokines (CCL2 and CXCL8) (17, 18). The reduction in the levels of IL-6, CCL2, and F_{ENO} induced by aerobic training in our study is also consistent with results of previous studies in nonobese individuals with asthma (14, 19). However, we show for the first time a reduction in the levels of IL-4 and TNF and an increase in IL-10, supporting the antiinflammatory effects of exercise

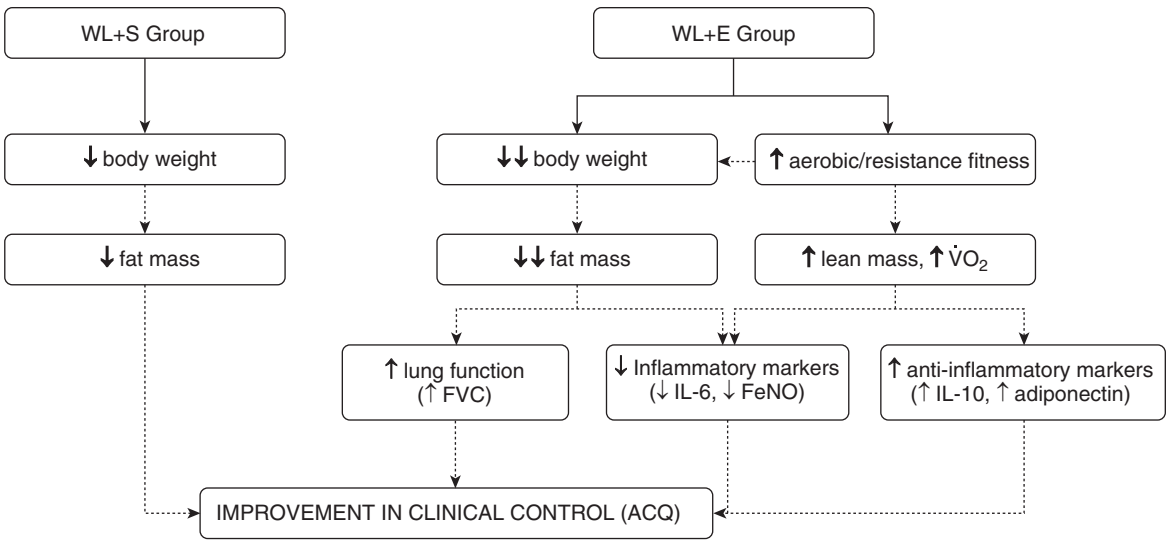

Figure 5. Possible mechanisms underlying the improvements in clinical asthma control (ACQ scores). *Solid lines* indicate effects of the intervention in each group. *Dashed lines* indicate significant linear correlations between variables. ACQ = Asthma Control Questionnaire; F_{ENO} = fractional exhaled nitric oxide; WL + E = weight-loss program plus aerobic and resistance exercise; WL + S = weight-loss program with sham exercise.

training on the pathophysiology of asthma as has been previously observed in animal models (16–18, 45). Interestingly, our study is also the first to demonstrate that exercise combined with caloric restriction increases the levels of 25(OH)D, likely caused by a reduction in visceral fat area and the increased availability of this fat-soluble vitamin (46). This finding is particularly relevant because vitamin D levels have been associated with asthma control and exacerbations (47) and seem to play a role in the interplay between obesity and asthma (48).

Surprisingly, although some differences were small in relative terms, in particular the changes in IL-4, they had highly significant effects. In our opinion, this may have occurred because although our obese patients with asthma did not present, on average, high levels of F_{ENO}, blood eosinophils, and/or IL-4, approximately 45% of them were IL-4 responders, showing higher levels of blood eosinophils and F_{ENO}, as previously demonstrated by Dias-Junior and coworkers (42). This finding reinforces the evidence suggesting that patients with the obese-asthma phenotype are not a uniform group and that their symptoms may involve both T-helper type 2–positive and T-helper type 2–negative inflammatory pathways (48, 49). Interestingly, for the patients who exercised, those who presented higher levels of inflammatory markers also presented reductions in F_{ENO} levels.

This study has some limitations. First, most of our population was female. However, asthma is predominantly observed in women (42, 50). Second, the strict inclusion criteria (including obesity grade II and moderate and severe asthma) may have limited the external validity of our findings. However, moderately obese subjects have more difficulty losing weight than those with mild obesity, and bariatric surgery is more frequently indicated for severely obese subjects (8). Furthermore, patients with a more severe disease seem to obtain the greatest benefit from the intervention (19, 42, 44). Another limitation of the present study is that the assessment of airway inflammation was restricted to assessing F_{ENO} and changes in other inflammatory patterns (e.g., neutrophil inflammation) could not be detected. Finally, the duration of the intervention may have been rather short for inducing behavioral changes in the patients. Nonetheless, the time frame was long enough for patients who exercised to achieve moderate weight loss accompanied by an important and significant improvement in the clinical control of their asthma. In addition, the weight loss was maintained after 6 months in both groups and after 1 year in the WL + E group.

In conclusion, we demonstrate that exercise training plays an important role in the integration of weight-loss lifestyle interventions aimed at improving the clinical control of asthma by changing body composition (reducing fat mass and increased free fat mass) and increasing aerobic fitness. The mechanisms by which weight loss improves asthma control are not fully understood. Our results clearly suggest that weight loss contributes to improving asthma, at least in part, by ameliorating lung function and inflammatory biomarkers. Furthermore, the increase in physical capacity influences inflammatory and antiinflammatory pathophysiologic pathways that contribute to asthma. These findings suggest that adding exercise to nutritional and psychological therapies is a useful strategy for effectively achieving clinical control of asthma in obese patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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