Effects of weight loss on asthma control in obese patients with severe asthma

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Abstract

Studies on the effects of weight loss in patients with asthma are scarce. No studies have been done in patients with severe asthma. To assess the impact of weight loss in patients with severe asthma associated with obesity.

Open, prospective, randomized study of 2 parallel groups, in patients with severe uncontrolled asthma and moderate obesity. The primary outcome was the level of asthma control 6 months after initiation of the weight reduction program quantified by the Asthma Control Questionnaire (ACQ). We evaluated clinical parameters, and lung function, markers of airway inflammation and circulating cytokines.

Twenty-two patients were randomized to undergo treatment for obesity, and 11 as the control group. The weight reduction program was associated with significant improvements in asthma control (ACQ mean ± SE; 3.02 ± 0.19 to 2.25 ± 0.28 in the treatment group *vs* 2.91 ± 0.25 to 2.90 ± 0.16 in the controls, *P* = 0.001). This improvement was not accompanied by changes in markers of airway inflammation or bronchial reactivity, but by an increase in forced vital capacity.

Our results suggest that weight reduction in obese patients with severe asthma improves asthma outcomes by mechanisms not related to airway inflammation.

Key words

Asthma, obesity, weight loss.

Summary Sentence: Weight loss improves outcomes in severely asthmatic obese patients. Poor asthma control results from obesity-related factors.

Abbreviations

ACQ: Asthma Control Questionnaire

ACT: Asthma control test

BMI: body mass index

ITT: intent-to-treat

PP: per protocol

SGRQ: St. George's Respiratory Questionnaire

Introduction

Severe asthma affects less than 10% of asthmatic patients, but has a disproportionate impact on the use of health resources, contributing to at least half of the direct and indirect costs of the disease [1, 2]. An important component of the management of these patients is the correct diagnosis and treatment of comorbid or associated conditions that may influence asthma control.

The proportion of obese or overweight individuals is elevated in patients with severe asthma [3]. In the TENOR study [3], the mean body mass index (BMI) of adult patients was 30.4 kg/m^2. More than half of patients with severe asthma treated at our centre are obese [4]. In fact, obesity is a risk factor for asthma [5] and is associated with the severity of the disease [6], a poor response to corticosteroids [7,8] and worse clinical control [9,10] represented by more days with symptoms, more visits to the emergency room, greater use of rescue medication, and greater loss of work days [6].

Several hypotheses [11] have been proposed to explain the relationship between obesity and asthma severity and control. First, obesity has unfavourable mechanical effects on lung function. Second, it is associated with a number of comorbid factors that might interfere with asthma control, such as dietary intake, decreased physical activity, gastroesophageal reflux, and obstructive sleep apnoea. A further possible mechanism relates to the chronic mild systemic inflammation associated with obesity potentially increasing airway inflammation.

Studies on the effects of weight loss in patients with asthma are still scarce. In a systematic review [11], only 5 of 15 studies considered relevant by the authors

reported asthma markers as outcomes. The only randomized controlled trial found, conducted in subjects with mild to moderate asthma, reported improvement in pulmonary function parameters, fewer asthma symptoms, and improved quality of life in those who lost weight with clinical treatment [11]. More recently, Dixon et al [12], prospectively, investigated the role of loss of weight induced by bariatric surgery in the pathophysiology of asthma. They showed that the weight reduction was associated with better clinical control, without changes in the cellularity of bronchoalveolar lavage, but with decreased airway responsiveness in those who had normal levels of IgE. None of these studies included patients with severe asthma.

This study reported herein was designed to assess the impact of weight loss with a medical weight loss program in patients with severe asthma associated with obesity. Our hypothesis was that weight reduction would result in better asthma control. To test it, we conducted an open, prospective, randomized study of 2 parallel groups, of 6-months duration, that evaluated the effects of a weight reduction program on clinical parameters, as well as lung function, markers of airway inflammation, and circulating cytokines in patients with severe asthma and moderate obesity.

Methods

Setting and participants

This was a prospective open study with 2 randomized parallel groups. The participants were obese (BMI ≥ 30 kg/m^2) and with severe asthma (Online Repository). The local institutional review board approved this study, and all patients provided written informed consent. The study is registered on ClinicalTrials.gov as NCT 01049657.

Design overview

The patients were selected to participate in the study if their asthma was not controlled according to GINA criteria [13] after a 3-month run-in period, during which medication adherence was checked, and influence of exogenous or endogenous aggravating factors was evaluated. Eligible patients were randomized by computer-generated randomization in blocks in a 2:1 ratio (weight loss:control).

The weight-loss programme consisted of low caloric intake, use of sibutramine (10mg per day) (patients with any cardiovascular risk were excluded) and orlistat (maximum dose of 120mg per day). The principles and behaviour methods of this weight reduction programme are described elsewhere [14]. All participants attended bimonthly consultations in the asthma clinic, where they were seen by the same investigator (SADJ), had the use of the device checked, and compliance with medication assessed by a count of the remaining doses, received the same amount of education about asthma [15], and were followed for 6 months.

Outcome measures

The primary outcome measure was the level of asthma control 6 months after initiation of the weight reduction program quantified by using the Asthma Control Questionnaire (ACQ) [16].

Secondary clinical outcomes included the Asthma Control Test (ACT) [17], lung function results, score on the St. George's Respiratory Questionnaire (SGRQ) [18], change in methacholine reactivity (in participants with an FEV_1 that was 50% or more of predicted value), daily use of asthma reliever medication, percentage of asthma symptom-free days, number of visits to the emergency room and exacerbations, and the score on the Gastroesophageal Reflux Disease-Health-Related Quality-of-Life Scale [19].

Markers of airway cellular inflammation were measured in induced sputum [20] and with exhaled nitric oxide (NIOXMINO - Aerocrine AB, Solda, Sweden). IgE, C-reactive protein, leptin, eotaxin, and Transforming Growth Factor beta 1 (ELISA - R&D System Inc., Minneapolis, MN, EUA) levels in serum were also measured.

Statistical analysis

The study was powered on the assumption that the ACQ score would show a difference of 0.5 between the groups. Assuming a type I error rate of 0.05, 11 participants would provide greater than 80% power to detect a significant difference.

The intent-to-treat (ITT) population included all patients randomized who concluded the 6-month follow-up. The per protocol population (PP) was defined as the patients who lost at least 10% of their body weight.

The results are expressed in absolute and percentage for qualitative variables, as mean and standard error for the variables normally distributed, and median, minimum, maximum, interquartiles for non-normally distributed data.

We used a *t* test, the Fisher exact test, or the Mann-Whitney test to compare differences between the groups. Repeated-measures ANOVA was used to compare changes in measures from baseline to 6 months after initiation of the weight reduction program. We studied the difference between study groups, the time effect

and the interaction between group and time effect. The Mann-Whitney test was used to compare between the groups and the Friedman test to compare within each group.

A descriptive level of $P < 0.05$ was adopted for all tests.

Results

Baseline characteristics

Thirty-seven patients met the criteria for inclusion in the study; 33 were randomized (Figure 1). Of the 22 patients randomized to undergo treatment for obesity, 12 achieved the weight loss goal of at least 10% of body weight.

The characteristics of patients at baseline are shown in Table 1 and Table E1 – Online Repository. The group consisted predominantly of women with moderate obesity and severe uncontrolled asthma, despite the use of high doses of controller medication (median dose of budesonide of 1600 g/d). Most patients reported that they were diagnosed with asthma in childhood or adolescence. They disclosed a functional pattern of moderate airflow obstruction, air trapping, and increased airway resistance. The baseline values of inflammatory markers in sputum showed a marked eosinophilia. The increased serum levels of IgE were consistent with a predominance of atopic asthma.

Table 1: Baseline demographic, clinical and pulmonary function data, and markers of inflammation and IgE level of study patients – Intent-to-treat analysis.*

	Control group	Treatment group	*P* value
No.	11	22	
Age (y)[†]	44 (24)	42 (15,75)	0.825
Female sex (%)	100	90.9	0.542[‡]
BMI (kg/m^2)	37.29 ± 1.07	39.68 ± 1.31	0.243[‡]
ACQ	2.91 ± 0.25	3.02 ± 0.19	0.718[‡]
Age of asthma onset (y)[†]	12 (19)	10 (25)	0.795
Duration of asthma (y)[†]	32 (27)	27 (23.75)	0.821
ICU admission (no.)[†]	1(2)	0(1)	0.233
Rhinitis (%)	90.9	77.3	0.407[‡]
Gastroesophageal reflux disease (%)	81.8	59.1	0.258[‡]
Pack-year smoking (no.)	3.86 ± 1.12	4.50 ± 1.44	0.437[‡]
Budesonide dose (g/d)[†]	1600 (800)	1600 (0)	0.985
Formoterol dose (%)	100	100	>0.999
Omeprazole dose (mg)[†]	80 (0)	80 (0)	>0.999
Leukotriene modifier (%)	72.7	40.9	0.141[‡]
FEV$_1$ (% predicted)	59.2 ± 4.2	65.7 ±2.7	0.105
FVC (% predicted)	74.5 ± 1.5	80.5 ± 2.8	0.053
FEV$_1$/FVC	0.64 ± 0.04	0.67 ± 0.02	0.635
TLC (% predicted)	111.2 ± 3.3	106.5 ± 3.8	0.756
RV (% predicted)	186.4 ± 13.7	153.0 ± 8.4	0.043
RV/TLC	0.53 ± 0.03	0.45 ± 0.02	0.006
Raw (cmH$_2$0/L/s)	4.69 ± 0.58	3.63 ± 0.33	0.177
FeNO (ppb)	20.1 ± 4.9	25.1 ± 3.1	0.089
Induced sputum eosinophils (%)	11.9 ± 3.9	13.9 ± 2.8	0.489

Induced sputum neutrophils (%)	41.7 ± 4.0	40.3 ± 4.4	0.450
Serum IgE (IU/mL)	409.18 ± 107.0	382.8 ± 56.7	0.344

Definition of abbreviations: BMI = body mass index; ACQ = asthma control questionnaire; ICU = intensive care unit; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity; TLC = total lung capacity, RV = residual volume; Raw = airway resistance; FeNO = nitric oxide fraction in exhaled air.

* Values shown are means and SEs unless otherwise stated. *P* values shown are for ANOVA.

[†] Values shown are median (interquartile difference). *P* values shown are for Mann-Whitney test.

[‡] *P* values shown are for Fisher exact test.

Effect of weight reduction on asthma control

The average reduction in weight in the treatment group was 7.88 kg, corresponding to 7.5% of baseline weight. The BMI decreased significantly in the treatment group and remained unchanged in the control group. The ITT analysis also showed improvement in the control as measured by ACQ, but did not detect changes in ACT and SGRQ (Table E2 - Online Repository). Weight reduction in per protocol analysis resulted in a statistically and clinically significant improvement in asthma control, measured by ACQ, ACT, and SGRQ (Table 2).

Table 2 – Clinical outcomes of study patients before and 6 months after weight reduction– Per protocol analysis.

	Control group (n=11)			Treatment group (n=12)		
	Visit 0	Visit 6	*P* value*	Visit 0	Visit 6	*P* value*
BMI (kg/m^2)	37.29 ± 1.07	36.85 ± 1.06	NS	39.88 ± 1.85	34.58 ± 1.74	<0.001[†]
ACQ	2.91 ± 0.25	2.90 ± 0.16	NS	3.04 ± 0.25	1.64 ± 0.19	<0.001[†]
ACT	11.18 ± 1.15	12.09 ± 0.65	NS	12.25 ± 1.08	17.42 ± 1.11	<0.001[‡]
SGRQ						
Symptoms	57.41 ± 5.97	53.85 ± 6.74	NS	62.41 ± 5.19	55.12 ± 7.54	NS
Activity	82.43 ± 2.86	81.17 ± 2.95	NS	79.63 ± 4.58	59.97 ± 5.14	<0.001[§]
Impact	61.65 ± 4.88	54.40 ± 4.28	NS	57.69 ± 2.89	34.18 ± 4.71	<0.001[‖]
Total	67.29 ± 3.37	62.42 ± 3.27	NS	65.12 ± 3.02	45.47 ± 4.42	<0.001[**]
GERD-HRQL	8.00 ± 2.93	10.38 ± 2.12	NS	8.20 ± 2.26	8.50 ± 1.55	NS

Definition of abbreviations: BMI = body mass index; ACQ = asthma control questionnaire; ACT = Asthma Control Test, SGRQ = St. George Respiratory Questionnaire; GERD-HRQL = Gastroesophageal Reflux Disease-Health-Related Quality-of-Life Scale.

 * *P* values shown are for ANOVA.

[†] *P* < 0.001 for the comparisons between the groups.

[‡] *P* = 0.024 for the comparisons between the groups.

§ *P* = 0.005 for the comparisons between the groups.

[‖] *P* = 0.028 for the comparisons between the groups.

** *P* = 0.011 for the comparisons between the groups.

There was symptomatic improvement in these individuals, represented by the increase in symptom-free days (P = 0.022; PP analysis), less use of rescue medication (P = 0.002; PP analysis), and fewer visits to the emergency room (P = 0.0095; PP analysis) during the study period. There were no differences in the number of exacerbations. The quality of life related to gastroesophageal reflux also did not vary.

ACQ reached clinically significant improvements (> 0.5) in 11 of the 12 patients who lost at least 10% of their baseline weight, and in 3 of the 10 patients in the intervention group who did not reach the target weigh loss (Figure 2).

Effect of weight reduction on lung function tests

Pulmonary function is shown in Table 3 (and Table E3 - Online Repository). The forced vital capacity increased significantly in the treatment group and remained unchanged in the control group. Forced vital capacity was significantly improved in patients in the intervention group who lost > 10% of their baseline weight, but not in the patients who did not reach the target weigh loss (Figure 3). There was a trend toward a correlation between the change in ACQ and the change in FVC (r= - 0.38; p=0.082). The other measures showed no differences between groups.

Table 3 – Pulmonary function of study patients before and 6 months after weight reduction – Per protocol analysis.

	Control group (n=11)			Treatment group (n=12)		
	Visit 0	Visit 6	P value*	Visit 0	Visit 6	P value*
FEV_1 (L)	1.64 ± 0.13	1.67 ± 0.12	NS	1.85 ± 0.15	2.01 ± 0.15	NS
FEV_1 (%)	59.2 ± 4.2	61.5 ± 3.2	NS	64.08 ± 3.35	70.00 ± 4.89	NS
FVC (L)	2.55 ± 0.11	2.48 ± 0.12	NS	2.92 ± 0.17	3.16 ± 0.16	0.002[†]
FVC (%)	74.5 ± 1.5	74.4 ± 2.0	NS	82.42 ± 3.16	87.75 ± 2.99	NS
FEV_1/FVC	0.64 ± 0.04	0.67 ± 0.03	NS	0.64 ± 0.03	0.64 ± 0.04	NS
$FEF_{25=75\%}$ (L)	1.08 ± 0.18	1.09 ± 0.15	NS	1.13 ± 0.21	1.32 ± 0.23	NS
$FEF_{25=75\%}$ (%)	37.6 ± 6.3	39.18 ± 5.39	NS	36.75 ± 5.70	44.92 ± 6.78	NS
IC (L)	2.16 ± 0.11	2.03 ± 0.17	NS	2.49 ± 0.17	2.45 ± 0.19	NS
IC (%)	96.7 ± 5.6	93.5 ± 7. 5	NS	109.00 ± 6.08	103.42 ± 7.25	NS
TLC (L)	5.54 ± 0.29	5.22 ± 0.19	NS	5.70 ± 0.26	5.80 ± 0.36	NS
TLC (%)	111.2 ± 3.3	107.2 ± 4.5	NS	113.50 ± 4.71	111.92 ± 4.76	NS
ERV (L)	0.44 ± 0.07	0.38 ± 0.07	NS	0.40 ± 0.09	0.73 ± 0.17	NS
ERV (%)	41.1 ± 6.6	33.9 ± 6.1	NS	35.75 ± 11.60	63.67 ± 19.45	NS

RV (L)	2.96 ± 0.28	2.69 ± 0.19	NS	2.80 ± 0.26	2.62 ± 0.32	NS
RV (%)	186.4 ± 13.7	171.0 ± 14.0	NS	168.33 ± 10.60	158.75 ± 17.54	NS
RV/TLC	0.53 ± 0.03	0.51 ±0.03	NS	0.49 ± 0.03	0.44 ±0.03	NS
Raw (cmH$_2$O/L/s)	4.69 ± 0.58	4.10 ± 0.54	NS	3.44 ± 0.40	3.63 ± 0.39	NS
Raw (%)	257.5 ± 31.0	220.4 ± 29.0	NS	188.00 ± 21.17	202.75 ± 20.57	NS
Gaw (L/s/cmH$_2$O)	0.16 ± 0.03	0.09 ± 0.02	NS	0.16 ± 0.03	0.09 ± 0.01	NS
Gaw (%)	31.8 ± 6.6	43.2 ± 8.1	NS	42.33 ± 6.80	43.08 ± 6.79	NS

Definition of abbreviations: FEV$_1$ = *forced expiratory volume in the first second;* FVC = *forced vital capacity;* FEF$_{25=75\%}$ = forced expiratory flow between 25% and 75% of vital capacity; IC = inspiratory capacity; *TLC = total lung capacity; ERV = expiratory reserve volume; RV = residual volume; Raw = airway resistance; Gaw = airway conductance.*

* *P* values shown are for ANOVA.

[†] P = 0.006 for the comparisons between the groups.

Effect of weight reduction on airway hyperresponsiveness and on markers of airway and systemic inflammation

Airway hyperresponsiveness, exhaled nitric oxide levels, and induced sputum cellularity did not change throughout the study.

Leptin levels decreased in both groups (P = 0.013 comparing baseline and 6 months, independent of the group). Serum levels of IgE, C-reactive protein, eotaxin, and TGF-β1 did not change (Table 4 and Table E4 - Online Repository).

Table 4 – Airway responsiveness, markers of inflammation and IgE level of study patients before and after weight reduction – Per protocol analysis.

	Control group (n=11)			Treatment group (n=12)		
	Visit 0	Visit 6	*P* values *	Visit 0	Visit 6	*P* values *
PD$_{20}$ (mg) [†‡]	0.35 (0.36)	0.89 (2.58)	NS	1.10 (2.65)	2.30 (13.55)	NS
FeNO (ppb)	20.1 ± 4.9	19.3 ± 3.2	NS	19.6 ± 3.7	26.8 ± 5.2	NS
Induced sputum eosinophils (%)	11.9 ± 3.9	12.5 ± 3.2	NS	15.0 ± 4.9	14.4 ± 4.7	NS
Induced sputum neutrophils (%)	41.7 ± 4.0	53.6 ± 4.1	NS	40.2 ± 5.8	41.9 ± 7.3	NS
Induced sputum lymphocytes (%) [†]	3.0 (4.0)	3.0 (4.0)	NS	2.0 (4.0)	2.0 (2.0)	NS
Induced sputum macrophages (%)	20.3 ± 4.6	12.5 ± 3.4	NS	17.4 ± 3.1	17.3 ± 3.9	NS
Induced sputum epithelial cells (%)	22.4 ± 5.9	17.7 ± 5.3	NS	24.4 ± 6.5	23.8 ± 6.3	NS
Serum IgE (IU/mL)	409.1 ± 107.0	507.5 ± 124.3	NS	268.5 ± 62.0	292.8 ± 80.7	NS
Serum C-reactive protein (mg/L)	10.3 ± 2.6	15.0 ± 4.3	NS	8.5 ± 2.4	9.3 ± 2.4	NS

Serum leptin (ng/mL)	52.7 ± 5.3	41.4 ± 7.2	NS	66.2 ± 10.0	37.9 ± 5.8	NS
Serum eotaxin (pg/mL)	116.1 ± 28.8	118.15 ± 23.86	NS	101.6 ± 25.2	106.1 ± 23.4	NS
TGFβ1 (pg/mL) [†]	2652.5 (311.7)	2482.7 (2688.6)	NS	2620.8 (287.8)	2658.8 (2529.1)	NS

Definition of abbreviations: PD_{20} – provocative dose of methacholine required to achieve 20% fall in forced expiratory volume in the first second; FeNO = nitric oxide fraction in exhaled air; TGFβ1 = Transforming Growth Factor beta 1.

*P values shown are for ANOVA.

[†] Values shown are median (interquartile difference). *P* values shown are for Mann-Whitney test.

[‡] N = 10 in the treatment group; two patients had FEV_1 less than 50% of predicted.

Discussion

In this prospective trial conducted in obese patients with severe asthma, a weight reduction program was associated with improvements in asthma control. This improvement was not accompanied by changes in markers of airway inflammation or bronchial reactivity, but by an increase in forced vital capacity. This result suggests that weight loss has an important role in the treatment of obese difficult-to-control asthmatic subjects.

Our results add to the published medical literature, demonstrating the importance of obesity and its treatment in the management of patients with severe asthma.

In this study, the group of patients included those who belong to the low-income group of a developing country, was composed mainly of women with moderate obesity, with early onset severe asthma, markedly uncontrolled despite high doses of maintenance medication, with decreased pulmonary function, high morbidity, poor health-related quality of life, high levels of serum IgE and eosinophilic airway inflammation. Several authors [21-24] have suggested that obesity-associated asthma is different from asthma found in nonobese patients. Cluster analysis in the United States cohort of severe asthma patients [24] identified a group of mostly older obese women with late-onset nonatopic asthma, moderate reductions in FEV_1 and frequent oral corticosteroid use to manage exacerbations. In their analysis of a dataset of patients with a diagnosis of refractory asthma in the United Kingdom, Haldar et al [23] described an obese subgroup with a female preponderance, evidence of asthma symptoms, and an absence of eosinophilic airway inflammation. Others did not find direct evidence of an airway inflammatory profile that is specific to obesity [25]. Actually, the patients included in our study best

fit the early-onset atopic asthma type, with greater airway dysfunction, symptoms, and eosinophilic airway inflammation on a high dose of corticosteroid [23]. We speculate that the phenotype described from the database of patients from developed countries, particularly the most severe, may not be universally applicable in scenarios of patients from a different background.

To the best of our knowledge, there are no previous prospective randomized studies showing the benefit of a medical weight loss program on asthma outcomes in obese severely asthmatic patients such as those included in this study. In their meta-analysis of studies on weight loss and asthma in obese patients, Eneli and al [11] found 3 observational studies and only 1 randomized trial that used low-calorie diets or a medical weight loss program, all in patients with mild or moderate asthma. Stenius-Aarniala et al [26] conducted a 1-year randomized controlled trial using low-calorie diets and reported that weight reduction improved lung function, symptoms, morbidity, and health status. Patients with severe asthma were excluded from the study. In regard to bariatric surgery for asthma patients, Dixon et al [12] reported that asthmatic participants had significant improvements in asthma control and asthma quality of life.

The statistically and clinically significant improvement in asthma control measured by ACQ found in our study was not observed in recently published observational studies of patients with refractory or difficult-to-control asthma. Bafadhel et al [27] followed 129 patients with refractory asthma for 12 months, of whom 74% of patients had an elevated BMI (with characteristics very similar to those of our patients) and 77% of patients had a change in weight of ± 2kg after 1 year. Fifty-four per cent of patients had a mean (SD) increase in weight of 4.9 (2.9) kg, and 23% of patients had a mean (SD) decrease in weight of 4.4 (2.8) kg. Compared to

baseline, there was no difference after 1-year follow-up in lung function, maintenance corticosteroid, inhaled corticosteroid dosage, ACQ scores, or eosinophilic airway inflammation in men or women that lost weight, gained weight, or did not change their weight. Haselkorn et al [28] analysed the effects of weight change on asthma control, asthma-related quality of life, number of steroid bursts, and exacerbation of asthma symptoms in a population of adult patients with severe or difficult-to-treat asthma who participated in the TENOR study. Asthma patients who gained > 5 lb (2.27 kg) during the 12-month interval between baseline and follow-up reported poorer asthma control, worse quality of life, and a greater number of steroid bursts than patients who maintained their baseline weight or lost < 5 lb. The study did not identify improved outcomes with weight loss. The authors explain that their choice of the 5-lb cut off was the largest weight cut off they could use while making estimates of the effects with reasonable precision. In addition, 5 lbs was deemed to be a low, yet reasonable and actionable, cut point that physicians could easily communicate to their patients.

Getting patients to loose weight is undoubtedly a difficult task; only 12 out of 22 volunteers assigned to the treatment group in the present study reached the target loss of at least 10% of the baseline weight. In these patients, the mean weight loss of 14.04 kg (13.3% of baseline weight) was accompanied by a statistically and clinically significant decrease of 1.40 in the ACQ score (PP analysis), compared with a mean reduction in weight of 7.88 kg (7.5% of baseline weight), resulting in a decrease of 0.77 in the ACQ score in the ITT analysis of the 22 patients allocated to the treatment group. Our results are in accordance with those of Scott et al [29] who suggest a weight loss goal of 5-10% be recommended to assist in the clinical management of overweight and obese adults with asthma. Taking into account our

results and those of other authors, it is reasonable to conclude that obese patients with asthma of any severity will improve asthma control provided they lose an appropriate percentage of their baseline weight [26-29]. Considering that despite the improvement observed in our patients, their average ACQ remained consistent with poor control (> 1.5); on the other hand, even those patients who lost more than 10% of their weight remained obese. We can therefore speculate that reaching a normal weight would lead to asthma control in a substantial proportion of these patients.

Our study has some limitations. The nature of the intervention did not allow our study to remain blinded. The control group did not receive a placebo or control intervention, which could have the effect of allowing overestimation of the effect size. After randomization, patients in the control group may have been disappointed, which could influence their assessment of symptoms and quality of life. Apart from the weight reduction program, the control group received equal attention from the medical staff, as well as assured access to a weight reduction program similar to that applied in the treatment group at study completion. The female predominance observed in our severe asthmatic population was previously reported [4]. The 2 men included in our study were randomized to the intervention group, reached the initial goal of at least a 10% reduction in weight, and had clinically significant improvement in ACQ, suggesting that the effects of weight loss can also be extended to men.

It can be argued that the persistent eosinophilia despite high doses of inhaled corticosteroids may result from nonadherence to treatment, particularly when only 12 of the 22 patients assigned to the treatment group were compliant with the weight loss intervention. We have previously described persistent sputum eosinophilia despite steroid treatment not related to any specific clinical characteristic or to the inhaled corticosteroid dosage, in a cohort of patients similar to the cohort of the

present study [4]. This profile is in accordance with the results of Amelink et al. [30] who recently reported sputum eosinophilia in patients with severe asthma, despite the use of inhaled corticosteroids at doses equivalent to 1000 mcg of fluticasone. In another study, the same group described a "severe eosinophilic inflammation-predominant" cluster in which sputum eosinophilia was present despite treatment with medium-to-high doses of inhaled corticosteroids (in 26% of the cases combined with maintenance of oral corticosteroids) [31]. Taken together these data suggest that these patients characterize a specific asthma subphenotype. Whatever the explanation for this airway inflammation behavior, it does not interfere with the main conclusion of our study that indicates that weight reduction improves control in severe asthma patients by mechanisms independent of asthmatic inflammation.

Given the study design, it can be argued that the drugs used in the weight reduction program had some action on the mechanisms of asthma. There are no reports in the literature of such effects or drug interaction with bronchodilators or inhaled corticosteroids.

We recognize that a structured program of exercises is an integral part of the process of weight reduction. However, we have avoided deliberately encouraging patients to exercise to avoid including a confounding factor in the analysis of the results, given that aerobic exercise may interfere with the inflammatory response of the airways [32].

The results of this study are consistent with previous studies that suggest that poor asthma control in people who are obese is partially related to obesity related-factors, which are not reflected by traditional measures of asthma. In a recent published study, Farah et al [10] evaluated asthmatic patients at baseline and 12 weeks after high-dose inhaled corticosteroid treatment. They showed that at baseline

the independent predictors of ACQ results were FEV_1, exhaled nitric oxide, and BMI. After treatment, targeted against airway inflammation but not obesity, all patients improved irrespective of their weight. BMI became the sole independent determinant of asthma control. Studies in refractory asthma led to similar conclusions. In a cross-sectional evaluation of 139 obese and nonobese patients with difficult-to-treat asthma, van Veen et al [22] concluded that obesity was inversely related to sputum eosinophils and exhaled nitric oxide, and positively associated with the presence of comorbid factors and reduced lung volumes. In their 1-year observational study, Bafadhel et al [27] showed that change in weight was not associated with change in airway inflammation. Dixon et al [12] suggested that the influence of weight reduction on airway responsiveness might be related to IgE levels, because they observed improvement in airway responsiveness only in nonatopic patients.

Our study has clinical implications. We suggest that, in people who are obese and have severe asthma, increasing the doses of corticosteroids may not be the best therapeutic alternative for patients who maintain symptoms. Weight reduction in obese patients improves asthma control at least in part by attenuating the negative effects on lung volumes. Therefore, weight loss should be considered as a strategy to improve asthma control in these patients.

In conclusion, our study adds information to the controversy about the impact of obesity and its treatment on asthma control. Our results suggest that weight reduction in obese patients with severe asthma improves asthma outcomes by mechanisms not related to airway inflammation and that poor asthma control in people who are obese is at least in part the result of obesity-related factors. Although the sample analysed in our study was small, we can argue that the therapeutic

approach for obese patients with difficult-to-treat asthma should therefore be aimed at weight reduction as well as at optimizing anti-inflammatory treatment.

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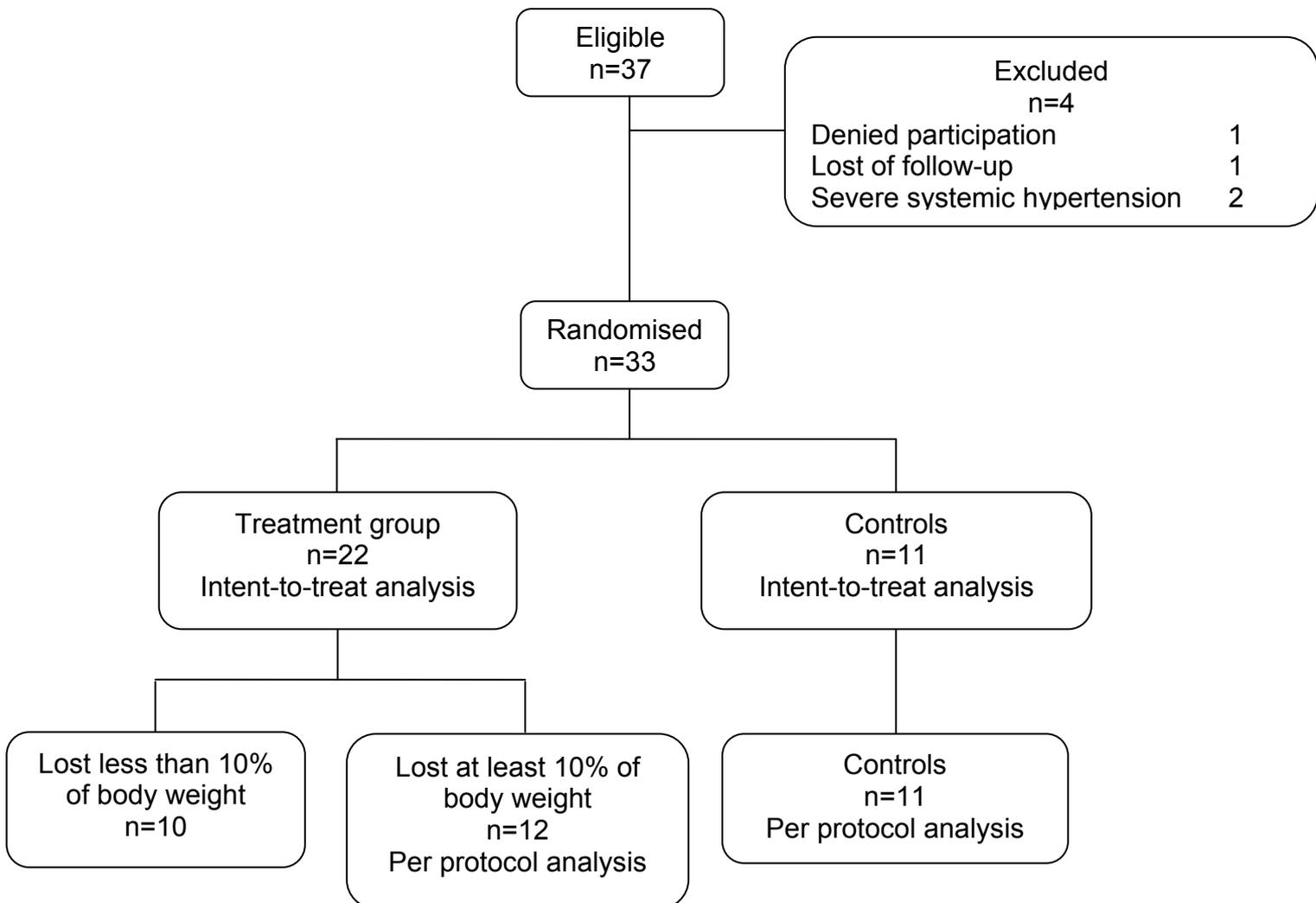
Figure 1 – Enrolment and follow-up of study patients.

Eligible
n=37

Excluded
n=4
Denied participation   1
Lost of follow-up   1
Severe systemic hypertension   2

Randomised
n=33

Treatment group
n=22
Intent-to-treat analysis

Controls
n=11
Intent-to-treat analysis

Lost less than 10%
of body weight
n=10

Lost at least 10% of
body weight
n=12
Per protocol analysis

Controls
n=11
Per protocol analysis

Figure 2 - Impact of degree of weight loss on asthma control questionnaire (ACQ)

p<0.05

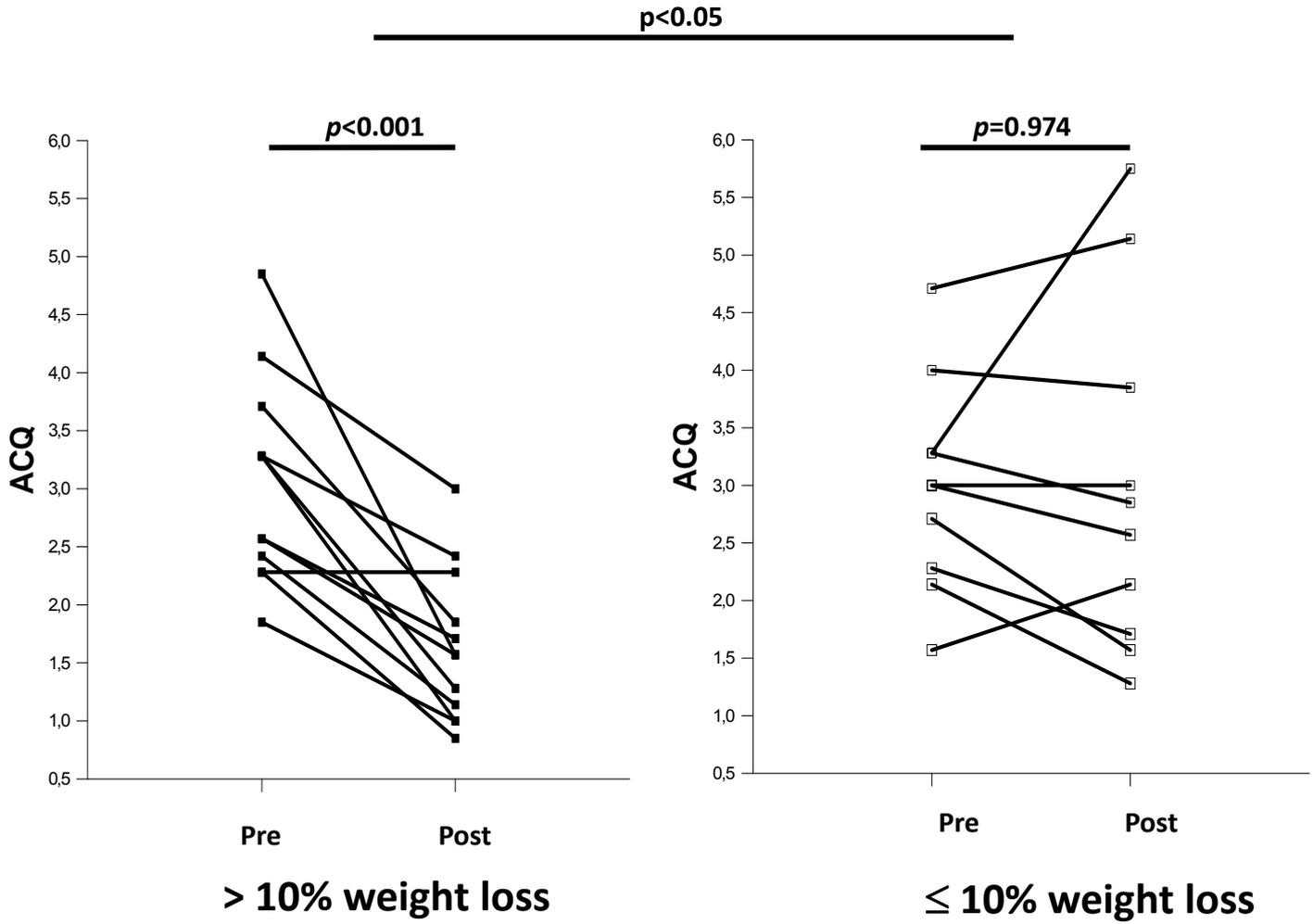*p*<0.001

p=0.974

> 10% weight loss

≤ 10% weight loss

Figure 3 - Impact of degree of weight loss on forced vital capacity (FVC)