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ORIGINAL ARTICLE

Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma

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▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/thoraxjnl-2014-206712).

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Received 18 December 2014
Revised 9 March 2015
Accepted 17 March 2015
Published Online First 1 May 2015

ABSTRACT

Background The pathogenesis of asthma in obese subjects is poorly understood and has been described as a specific phenotype in these patients. Weight loss improves asthma control and lung function. Whether this improvement is the result of better mechanical properties of the airways or decreased systemic and bronchial inflammation remains unclear.

Methods A longitudinal study in obese patients with asthma (bariatric surgery and asthma group (BS+A), n=27) and obese control (bariatric surgery without asthma group (BS−A), n=39) subjects undergoing bariatric surgery, and obese patients with asthma without intervention (no bariatric surgery and asthma group (NBS+A), n=12). Lung function, asthma control, cellular infiltrates in bronchial biopsies and circulating markers of systemic inflammation were measured during follow up at 3, 6 and 12 months.

Results Bariatric surgery resulted in a profound weight loss at 12 months. In the BS+A group as well as the BS−A group FEV_1, functional residual capacity, total lung capacity improved, whereas FEV_1/FVC only improved in the BS−A group. In addition, Asthma Control Questionnaire (ACQ), Asthma Quality of Life Questionnaire, inhaled corticosteroid use and PD_{20} improved in BS+A, whereas in the NBS+A group only ACQ improved. Small airway function R_5–R_{20} improved in both surgery groups, however the change in the BS+A group was greater, resulting in a comparable R_5–R_{20} between BS+A and BS−A at 12-month follow-up. Besides improvement of systemic inflammation (high sensitivity C-reactive protein, adiponectin and leptin) after BS, only a decrease in mast cell numbers was detectable in the BS+A group.

Conclusions Bariatric surgery improved small airway function, decreased systemic inflammation and number of mast cells in the airways. These effects could explain the improvement of asthma control, quality of life and lung function. Therefore bariatric surgery, in addition to all other positive effects, also improves asthma in subjects with morbid obesity.

Trial registration number 3204.

Key messages

What is the key question?

- Is the improvement of asthma control and lung function in obese subjects with asthma after bariatric surgery due to altered better mechanical properties of the airways or decreased systemic and bronchial inflammation?

What is the bottom line?

- Bariatric surgery improved not only small airway function, which could explain the improvement of asthma control, quality of life and lung function, but also induced a decrease in systemic inflammation and bronchial inflammation in morbidly obese subjects with asthma.

Why read on?

- This is the first study analysing bronchial biopsies in obese patients with asthma before and after bariatric surgery.

To cite: van Huisstede A, Rudolphus A, Castro Cabezas M, *et al*. *Thorax* 2015;**70**:659–667.

INTRODUCTION

Asthma prevalence has increased over recent decades,[1 2] concurrently with the prevalence of obesity, suggesting a possible link between obesity and asthma.[3] In a prospective study on the relationship between obesity and asthma, obese patients appeared to have a 2.6 times elevated risk of developing asthma.[4] In addition, obesity is associated with increased severity of asthma. Obese patients with asthma have worse asthma control[5] and respond less to standard therapy compared with lean patients with asthma.[6]

A recent position paper on weight loss interventions in asthma[7] concluded that the evidence for benefits from weight reduction on asthma outcomes is weak. Unfortunately, only studies with dietary weight loss were included, and a sustained effect of weight loss through lifestyle changes is small. In contrast, bariatric surgery leads to a more pronounced and persistent weight loss in subjects who are morbidly obese.[8] Therefore, weight loss by bariatric surgery may have more profound effects on asthma.

Asthma in patients who are obese has been described as a specific phenotype, with high symptom expression and late onset of symptoms.[9] Whether bronchial inflammation in obese subjects with asthma is characterised by eosinophilic or neutrophilic inflammation, or both, is a matter of debate in the literature. Different methods were

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used to (indirectly) measure bronchial inflammation. So far, only two studies have reported on the analysis of bronchial biopsies in obese subjects with asthma,[10 11] in which, especially in those who are morbidly obese, little inflammation was detectable in the airways. Although previous studies have shown that bariatric surgery does improve asthma control, lung function and systemic inflammation,[12–18] the effect on bronchial inflammation is unknown. Previous studies were conducted in small groups and either lacked follow up of a control group,[12 13 15] or they lacked a non-intervention control group.[13 14 16–18] To our knowledge, this is the first study analysing bronchial biopsies before and after bariatric surgery. We hypothesised that bariatric surgery and weight loss would result in improved bronchial obstruction, and reduced systemic and bronchial inflammation. To test this, we performed a cohort study to evaluate the impact of weight loss by bariatric surgery on asthma control, lung function and bronchial and systemic inflammation after 12-month follow-up. Baseline data (including subjects without 12-month follow-up) were published previously.[11]

METHODS

Study population

This study is part of a larger study, of which results have been reported before.[11 19] Inclusion and exclusion criteria of this study are described in the online supplementary material. In summary, subjects were between 18 and 50 years old, had a body mass index (BMI) above 35 kg/m^2, and were excluded if they smoked more than 10 cigarettes per day or had smoked more than 10 pack years.

The local ethics committee (Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o.) approved the study protocol (Netherlands Trial Register 3204), and all subjects gave written informed consent.

The subjects in this study were divided into three groups: a group of morbidly obese subjects with asthma scheduled for bariatric surgery (BS+A), a group of morbidly obese subjects without asthma also scheduled for bariatric surgery (BS−A), and a group of obese subjects with asthma not undergoing bariatric surgery (NBS+A). The first two groups were patients who applied for bariatric surgery in the Sint Franciscus Gasthuis; the third group was a control group included from our outpatient clinic.

The primary endpoint of the study was the change of FEV_1/FVC at 12-month follow-up. Secondary endpoints were other lung function parameters, asthma symptoms (asthma control, asthma-related quality of life, medication use), change of comorbidities (obstructive sleep apnoea syndrome (OSAS), gastro-oesophageal reflux disease) airway inflammation and systemic inflammation at 3, 6 and 12-month follow-up. Only subjects with a follow-up at 12 months were analysed. Baseline data (including subjects without 12-month follow-up) were published previously.[11]

Definition of asthma

Asthma was defined according to Global Initiative for Asthma (GINA) guidelines[1] as both the presence of symptoms and either an increase of ≥12% and 200 mL in FEV_1 after salbutamol, or a positive provocation test (methacholine PD_{20}<1.8 mg). Patients without airway reversibility and a negative provocation test formed the control group.

Descriptions of pulmonary function tests (spirometry,[20 21] exhaled nitric oxide,[22] impulse oscillometry, diffusion capacity[23] and methacholine provocation testing[24 25]) can be found in the online supplementary material, along with descriptions of the questionnaires used (Asthma Quality of Life Questionnaire (AQLQ)[26] and Asthma Control Questionnaire (ACQ)[27]), comorbidities (obstructive sleep apnoea syndrome (OSAS),[28] gastro-oesophageal reflux disease[29] and metabolic syndrome[30]), atopy definitions, laboratory measurements and the formula used for the percentage excess weight loss (%EWL).

Bronchial biopsies and immunohistochemistry

Peripheral bronchial biopsies were taken prior to laparoscopic bariatric surgery (either sleeve gastrectomy or Roux-and-Y gastric bypass), after routine anaesthesia with desflurane and remifentanil, directly after intubation.[11] Twelve months after bariatric surgery bronchial biopsies were taken during cosmetic surgery or during an outpatient visit. Bronchoscopy was performed according to the British Thoracic Society guidelines[31] using a flexible fibre optic bronchoscope (Olympus). Four biopsies were taken from the segmental carina from the right middle and lower lobe using a forceps (Boston Scientific, Radial Jaw 3). The 4 μm sections from paraffin-embedded bronchial biopsies were stained for EG2 (eosinophils), neutrophil elastase (neutrophils), AA1 (mast cells), CD68 (macrophages), CD20 (B cells), CD8, CD4 and CD3 (T cells), or negative control, and enumerated as cells per square millimetre submucosa on digitalised images. The smallest 10% of selected surfaces of biopsies were not used for analysis. The mean cell count of an individual was the mean of two to four biopsies. The observer was blinded with regard to the patient's number and clinical status during selection, processing and analysis of the biopsy samples. Baseline data were published previously.[11]

Power calculation and statistical analysis

The group size was powered on the expected change in FEV_1/FVC ratio after bariatric surgery. Based on a pilot study and published data we assumed that in the BS+A group the FEV_1/FVC ratio would increase from 72% to 75% (SD±6). The increase of 3% represents an effect size of 0.5. To find a difference in the group with obesity and asthma before and after operation with an α error of 5% and a power of 80%, we needed at least 27 participants per group. With an expected dropout of 25% over 1-year follow-up we aimed at 40 patients per subgroup.

For the comparison between the three groups at baseline, the independent samples median test for scaled data or the χ^2 or Fisher exact test were used. For all groups, baseline data were compared with 12-month follow-up data, using a non-parametric test (related-samples Wilcoxon signed rank test). Unless indicated otherwise, all data are expressed as median (min–max) for paired data for scale variables or percentage for categorical variables. Spearman correlation coefficient (R) was calculated. All analyses were performed using SPSS V.21.0 software (SPSS Inc., Chicago, Illinois, USA). Given the exploratory nature of this study, we did not control for multiple comparisons. Results were evaluated at 95% CI at a two-sided significance threshold of $p<0.05$.

RESULTS

A total of 101 patients were included in the initial study.[11] At 12-month follow-up data were available for 78 subjects, which were included in the present analysis. In table 1 (and online supplementary table S1B) the baseline subject characteristics are shown (27 BS+A, 39 BS−A and 12 NBS+A). There were no significant differences in demographic characteristics between the groups, with the exception of BMI.

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Table 1 Demographics of the study population

	NBS+A	BS+A	BS−A	p Value
Number				
Baseline	12	27	39	
3-month follow-up	11	26	33	
6-month follow-up	11	21	34	
12-month follow-up	12	27	39	
Gender (% female)	91.7%	74.1	82.1	0.494
Ethnicity (% non-Caucasian)	25.0%	14.8%	15.4%	0.714
Age (years)	33 (20–45)	36 (19–48)	39 (18–50)	0.440
Weight (kg)	103 (82–132)	130 (101–202)	126 (94–199)	0.044
Body mass index (kg/m^2)	35.6 (30.9–53.9)	45.1 (38.4–63.8)	43.1 (35.6–58.6)	0.015
Abdominal circumference (cm)	119 (102–155)	133 (112–165)	127 (103–200)	0.016
Smoking status				0.178
% never smoked	75.0%	55.6%	71.8%	
% stopped smoking	16.7%	11.1%	17.9%	
% current smoker	8.3%	33.3%	10.3%	
Pack years	0 (0–0)	0 (0–10)	0 (0–10)	0.311
Asthma				
Asthma Control Questionnaire*	1.7 (0.3–2.6)	1.1 (0.4–2.9)	0.3 (0–2.9)	<0.001
Asthma Quality of Life Questionnaire†	5.4 (3.5–6.7)	5.6 (3.7–6.8)	6.5 (3.7–7.0)	0.007
Lung function				
Spirometry				
FEV_1, pre (% predicted)	88 (45–106)	86 (66–119)	97 (73–125)	0.009
FEV_1, post (% predicted)	95 (49–106)	93 (75–118)	101 (75–129)	0.079
FVC, pre (% predicted)	102 (64–118)	97 (75–126)	106 (77–144)	0.575
FVC, post (% predicted)	107 (62–120)	99 (74–126)	107 (78–141)	0.754
FEV_1/FVC, pre (%)	79 (61–90)	76 (63–92)	81 (66–93)	0.096
FEV_1/FVC, post (%)	82 (69–91)	79 (67–94)	84 (68–94)	0.215
RV, post (% predicted)‡	79.5 (74–92)	74 (39–126)	74 (47–118)	0.567
TLC, post (% predicted)‡	92.5 (77–109)	98 (83–106)	95 (75–114)	0.826
FRC, post (% predicted)‡	68 (54–90)	62 (40–95)	64 (41–88)	0.554
RV/TLC, post (%)‡	26.5 (20–36)	22 (10–41)	24 (12–41)	0.146
Reversibility FEV_1	7 (−12–22)	9 (-6–20)	4 (-7–11)	0.012
Fe_{NO} (ppb)	17 (7–96)	16 (5–45)	16 (7–53)	0.870
Diffusion capacity, kCO (% predicted)	98 (70–116)	97 (69–133)	95 (69–134)	0.890
PD_{20} (mg)	0.31 (0.04–1.8)	0.37 (0.04–1.8)	1.8 (1.8–1.8)	
IOS				
R_5 (kPa/s)	0.58 (0.24–1.11)	0.69 (0.41–1.39)	0.57 (0.17–0.97)	0.022
R_{20} (kPa/s)	0.44 (0.20–0.65)	0.45 (0.27–1.03)	0.43 (0.18–0.68)	0.841
R_5–R_{20} (kPa/s)	0.18 (0.04–0.62)	0.25 (0.06–0.66)	0.17 (-0.1–0.48)	0.001
X_5 (kPa/s)	−0.16 (−0.67 to −0.1)	−0.26 (0.87 to −0.12)	−0.21 (−0.43 to −0.10)	0.138
F_{res} (Hz)	17.3 (9.2–30.4)	22.6 (10.7–28.9)	18.5 (8.4–28.7)	0.001

Data are presented as median (min–max).
*Scores of the Asthma Control Questionnaire range from 0 to 6, with lower scores indicating better asthma control.
†Scores of the Asthma Quality of Life Questionnaire range from 1 to 7, with higher scores indicating better asthma-specific quality of life.
‡Because of weight limitations for the body box (<150 kg), full spirometry could not be performed in all subjects; numbers for these parameters: NBS+A=4, BS+A=15, BS−A=30.
BS+A, bariatric surgery and asthma group; BS−A, bariatric surgery without asthma group; Fe_{NO}, exhaled nitric oxide; FRC, functional residual capacity; IOS, impulse oscillometry; NBS+A, no bariatric surgery and asthma group; PD_{20}, provocative dose of methacholine inducing a 20% fall in FEV_1; RV, residual volume; TLC, total lung capacity.

Weight loss

Sixty-three percent of the BS+A and 69% of the BS−A group underwent gastric sleeve resection; the remaining subjects underwent gastric bypass surgery. BMI and abdominal circumference decreased in both bariatric surgery groups, and remained stable in the non-intervention group (figure 1A,B). Although the %EWL was significantly lower in the BS+A group compared with the BS−A group (median 73% vs 84% respectively, p=0.045), the BMI did not differ between the BS+A and BS−A group at baseline or at 12-month follow-up.

Effect of weight loss on lung function tests

Figure 2 and table 2 show the results of the follow-up of lung function. Twelve months after bariatric surgery FEV_1/FVC and residual volume (RV) improved only in the BS−A group, whereas FEV_1 (post), functional residual capacity (FRC) and total lung capacity (TLC) improved in BS−A and BS+A groups. These results can be better explained by a reduction in lung restriction than by a reduction in lung obstruction. RV/TLC, representing hyperinflation, did not change in any of the groups. FEV_1/FVC, RV, FEV_1, FRC and TLC did not change in the NBS+A group, confirming that the improvement in restrict-

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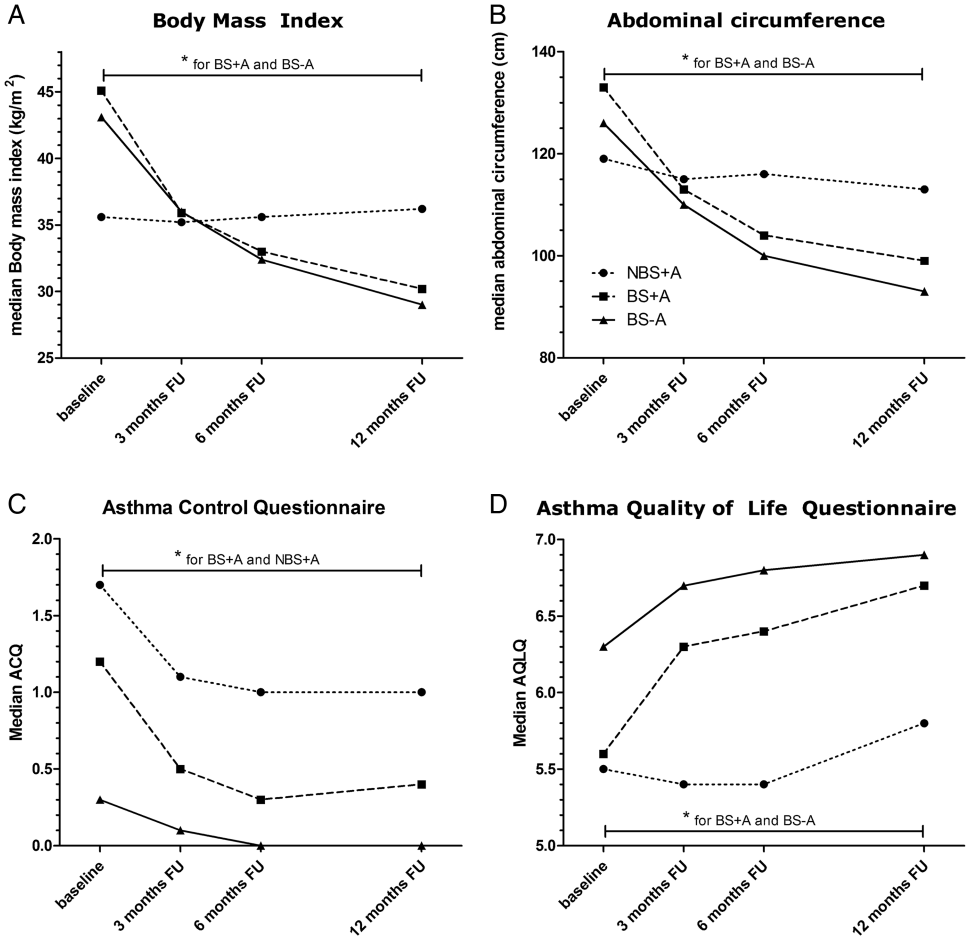

Figure 1 Effect of weight loss on asthma control. NBS+A, no bariatric surgery and asthma group (circles); BS+A, bariatric surgery and asthma group (squares); BS−A, bariatric surgery without asthma group (triangles). Only p values for comparison between baseline and 12-month follow-up were calculated; only significant p values are shown (*). Scores of the Asthma Control Questionnaire (ACQ) range from 0 to 6, with lower scores indicating better asthma control. Scores of the Asthma Quality of Life Questionnaire (AQLQ) range from 1 to 7, with higher scores indicating better asthma-specific quality of life. FU, follow-up.

ive lung function was due to weight loss. There was no significant change in diffusion capacity or exhaled nitric oxide (Fe_{NO}) in any of the groups.

Impulse oscillometry, and especially R_5–R_{20} as a measure of small airway function, showed a significant improvement in both bariatric groups (figure 2C). At baseline the BS+A group had a significantly higher R_5–R_{20} compared with the BS−A group ($p<0.001$). At 12-month follow-up the R_5–R_{20} of the BS+A group was comparable to the BS−A group. We found a correlation between BMI and R_5–R_{20} ($R=0.518$, $p<0.001$), and abdominal circumference and R_5–R_{20} ($R=0.415$, $p<0.001$). Also between ACQ and R_5–R_{20} ($R=0.498$, $p<0.001$) and ACQ and BMI ($R=0.374$, $p<0.001$) (figure 3).

In the BS+A group, 24 subjects had a positive provocation test at baseline ($PD_{20}<1.8$ mg). At 3, 6 and 12-month follow-up of these 24 subjects, 11 (of 24), 9 (of 20) and 13 (of 25) subjects had a negative provocation test, respectively. Median values increased significantly (figure 2D and table 2). In the NBS+A group the PD_{20} did not increase significantly. No correlation was found between PD_{20} and BMI, however we did found a significant correlation between PD_{20} and R_5–R_{20} ($R=-0.337$, $p<0.001$).

Effect of weight loss on asthma control

The ACQ improved statistically and was clinically significant ($\Delta>0.5$) in both asthma groups (NBS+A and BS+A) at 12-month follow-up (figure 1C). The improvement in ACQ in the BS−A group was also statistically significant, but not clinically significant.

The AQLQ did not improve in the NBS+A group, but it did improve in the BS+A group (statistically and clinically significant ($\Delta>0.5$)) at 12-month follow-up, and also in the BS−A group (figure 1D).

Medication use

In the BS+A group 10 subjects used inhaled corticosteroids (ICS) at inclusion in the study, of which 8 subjects agreed to stop for at least 6 weeks before provocation testing. Because of symptoms, one subject restarted ICS, and three subjects who did not use ICS before inclusion in the study were prescribed ICS because of progression of symptoms. So, a total of six subjects used ICS at baseline, with a median budesonide equivalence dose of 600 μg/day. At 12-month follow-up, ICS was prescribed to six subjects, however only four subjects used the ICS, with a median budesonide equivalence of 600 μg/ day.

In the NBS+A group all 12 subjects used ICS at baseline, and in follow-up all subjects remained on ICS: the median budesonide equivalence dose remained stable (baseline 800 μg, 3 months 400 μg and 12 months 800 μg).

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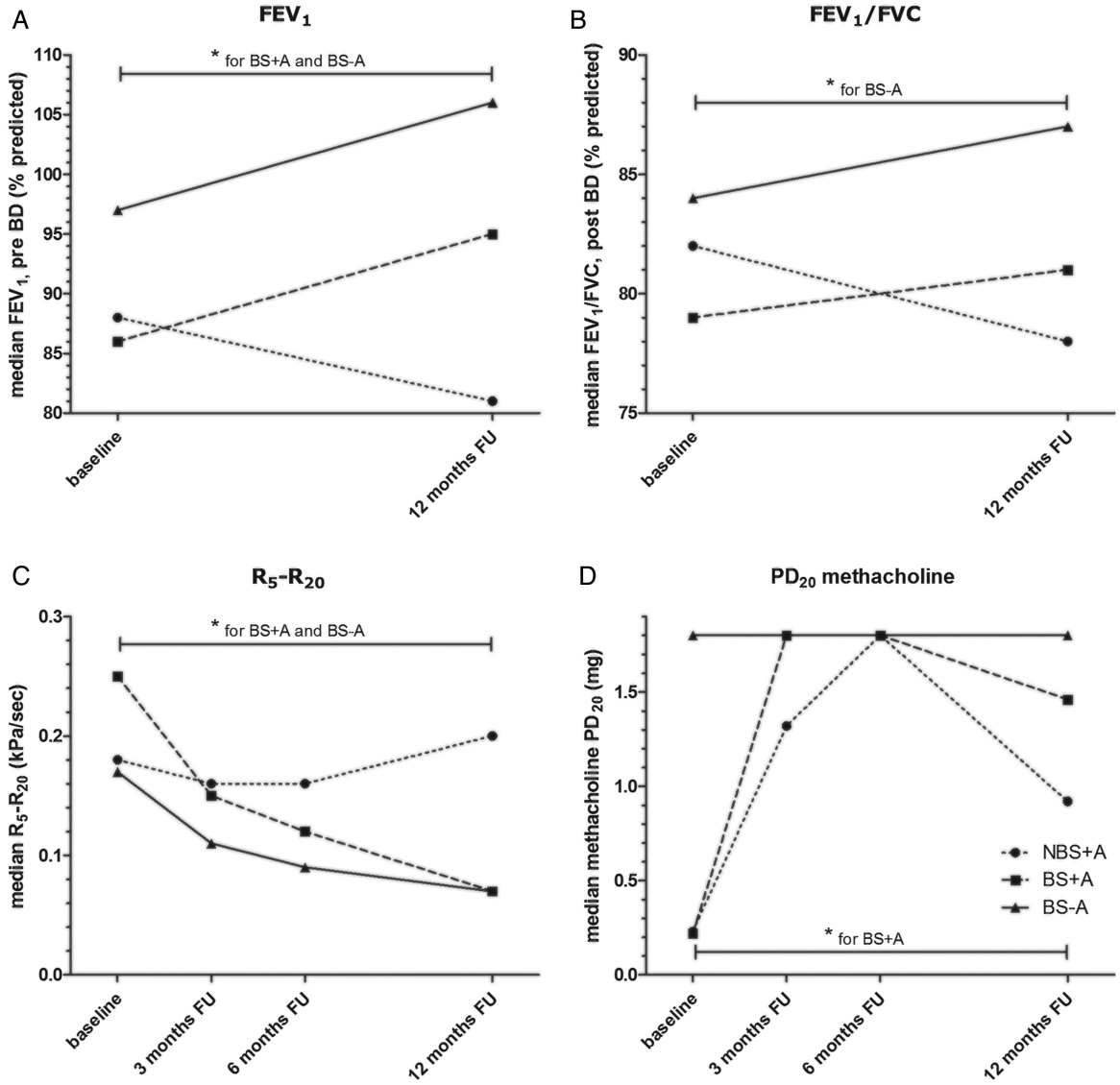

Figure 2 Effect of weight loss on lung function. NBS+A, no bariatric surgery and asthma group (circles); BS+A, bariatric surgery and asthma group (squares); BS−A, bariatric surgery without asthma group (triangles). Only p values for comparison between baseline and 12-month follow-up were calculated, only significant p values are shown (*). (A) FEV_1 BS+A median 86–95% predicted, p=0.001; BS−A median 97–106% predicted, p<0.001; (B) FEV_1/FVC BS−A 84–87%, p<0.001; (C) R_5–R_{20} BS+A 0.25–0.07 kPa/s, p<0.001; BS−A 0.17–0.07 kPa/s; p<0.001. While there was at baseline a significant difference in R_5–R_{20} between BS+A and BS−A group (p<0.001), at 12-month follow-up there was no significant difference (p=0.919); (D) PD_{20} BS+A median 0.22–1.46 mg, p=0.001.

Comorbidities and activity

There were no significant changes in the Epworth Sleepiness Scale or Gastro-oesophageal Reflux Disease questionnaire in any group at any follow-up time point (3, 6 or 12 months) (data not shown). Daily activity as assessed by the number of steps a day did improve significantly in both bariatric surgery groups at 12-month follow-up (BS+A: median 4946 to 8312, p=0.030; BS−A: median 5224 to 8094, p=0.005), and did not improve in the NBS+A group.

Effect of weight loss on bronchial and systemic inflammation

Interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α and granulocyte macrophage colony-stimulating factor (GM-CSF), markers of systemic inflammation, did not change at follow-up in any of the groups, although the levels of IL-6, TNFα and GM-CSF were at the lower limit of detection. Other markers of systemic inflammation, such as high-sensitivity C-reactive protein (hs-CRP), leptin and adiponectin, were significantly changed at 12-month follow-up in the BS+A and BS−A groups, and did not change in the NBS+A group (table 3).

At 12-month follow-up, bronchial biopsies were collected from 24 subjects (8 BS+A, 14 BS−A). Submucosal cell counts of eosinophils (EG2), neutrophils (NE), B cells (CD20), macrophages (CD68), CD4+ T cells or CD8+ T cells did not change at 12-month follow-up in either the BS+A or BS−A group (figure 4, and online supplementary table S4). In contrast, mast cells (AA1) decreased significantly at 12-month follow-up in the BS+A group (median 118–61 cells/mm^2, p=0.036), whereas CD3+ T cells decreased significantly at 12-month follow-up only in the BS−A group (median 884–558 cells/mm^2, p=0.015).

Subgroup analysis

When we divided the BS+A group into subjects who at baseline had a positive provocation test, and at 12-month follow-up

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Table 2 Effect of bariatric surgery on lung function

	NBS+A			BS+A			BS−A		
	Baseline	12-month FU	p Value*	Baseline	12-month FU	p Value*	Baseline	12-month FU	p Value*
Spirometry									
FEV_1, pre (% predicted)	88 (45–106)	81 (71–117)	0.553	86 (66–119)	95 (67–119)	<0.001	97 (73–125)	106 (75–134)	<0.001
FEV_1, post (% predicted)	95 (49–106)	88 (70–118)	0.759	93 (75–118)	100 (79–117)	0.001	101 (75–129)	108 (80–139)	<0.001
FVC, pre (% predicted)	102 (64–118)	103 (77–131)	0.683	96 (75–126)	105 (75–131)	0.001	106 (77–144)	109 (87–149)	0.009
FVC, post (% predicted)	107 (62–120)	106 (78–131)	0.721	99 (74–126)	107 (77–123)	0.002	107 (78–141)	107 (84–149)	0.046
FEV_1/FVC, pre (%)	79 (61–90)	78 (63–83)	0.550	76 (63–92)	77 (57–92)	0.246	81 (66–93)	83 (73–99)	0.021
FEV_1/FVC, post (%)	82 (69–91)	78 (66–86)	0.239	79 (67–94)	81 (69–94)	0.327	84 (68–94)	87 (77–98)	<0.001
RV, post (% predicted)†	79 (74–92)	65 (55–105)	0.285	80 (39–126)	79 (76–115)	0.789	72 (47–96)	82 (43–137)	0.013
TLC, post (% predicted)†	83 (77–102)	87 (74–105)	0.414	6 (83–106)	104 (79–115)	0.018	96 (75–114)	101 (81–122)	<0.001
FRC, post (% predicted)†	65 (54–90)	69 (61–85)	0.593	62 (40–95)	88 (53–117)	0.008	64 (41–77)	94 (59–145)	<0.001
RV/TLC, post (%)†	28 (25–36)	22 (20–40)	0.285	20 (10–41)	22 (15–29)	0.767	25 (15–33)	28 (11–40)	0.054
Fe_{NO} (ppb)‡	16 (7–96)	14 (8–58)	0.097	18 (8–45)	15 (8–32)	0.477	15 (7–53)	14 (5–67)	0.687
Diffusion capacity, kCO (% predicted)	98 (70–116)	95 (71–136)	0.202	97 (69–133)	99 (67–118)	0.483	95 (77–134)	91 (69–127)	0.179
PD_{20} methacholine (mg)	0.23 (0.09–1.31)	0.92 (0.19–1.8)	0.273	0.22 (0.04–1.40)	1.46 (0.04–1.8)	0.001			

Data are presented as median (min–max).
*p Value for comparison baseline versus 12-month follow-up within each group.
†Because of weight limitations for the body box (<150 kg), full spirometry could not be performed in all subjects; numbers for these parameters: NBS+A=3, BS+A=12, BS−A=27.
‡Log transformed for statistical purposes.
BS+A, bariatric surgery and asthma group; BS−A, bariatric surgery without asthma group; Fe_{NO}, exhaled nitric oxide; FRC, functional residual capacity; FU, follow-up; NBS+A, no bariatric surgery and asthma group; PD_{20}, provocative dose of methacholine inducing a 20% fall in FEV_1; RV, residual volume; TLC, total lung capacity.

either a positive (non-responder) or negative (responder) provocation test, we found no differences between the two groups. In a subgroup analysis of patients with low immunoglobulin E (IgE) ('T_H2-low', IgE<100, n=6) versus high IgE ('T_H2-high', n=12), we found that the PD_{20} only improved in the IgE-high group at 12-month follow-up (median 0.19–1.59 mg, p=0.003), and not in the IgE-low group (median 0.53–0.99 mg). We found no differences in change in R_5–R_{20}.

DISCUSSION

In the present study bariatric surgery of morbidly obese patients with asthma was found to result in a significant improvement in small airway function (R_5–R_{20}) and airway hyperresponsiveness (PD_{20} methacholine), as well as asthma control and markers of bronchial (mast cell counts) and systemic inflammation. In contrast, there was no change in FEV_1/FVC.

There was no significant improvement in our primary endpoint FEV_1/FVC, a marker of airway obstruction, in the BS+A group. However, in the BS−A group, there was a statistically significant increased FEV_1/FVC, showing that weight loss affects airway diameter to some extent in patients without asthma. As the power of this study should be adequate, we might conclude that weight loss does not influence obstruction of the larger airways in asthma subjects. In line with previous reports,[13 15] we found that weight loss induces an increase not only in TLC, but also FRC in both bariatric surgery groups, suggesting that the weight loss improves the relative restrictive lung function. Remarkably, the RV in the BS+A group did not change after bariatric surgery, whereas it did in the BS−A group. This could be because the RV at baseline was already relatively high in the BS+A group, so further improvement was unlikely. Perhaps the BS+A group had peripheral airway obstruction before bariatric surgery due to different fat distribution compared with the BS−A group, since the abdominal circumference is higher in the BS+A group. However, the RV/TLC ratio was the same in both bariatric groups, making a difference in obstruction less likely.

The main improvement in lung function was in R_5–R_{20}, a marker of small airway function. Whereas at baseline the R_5–

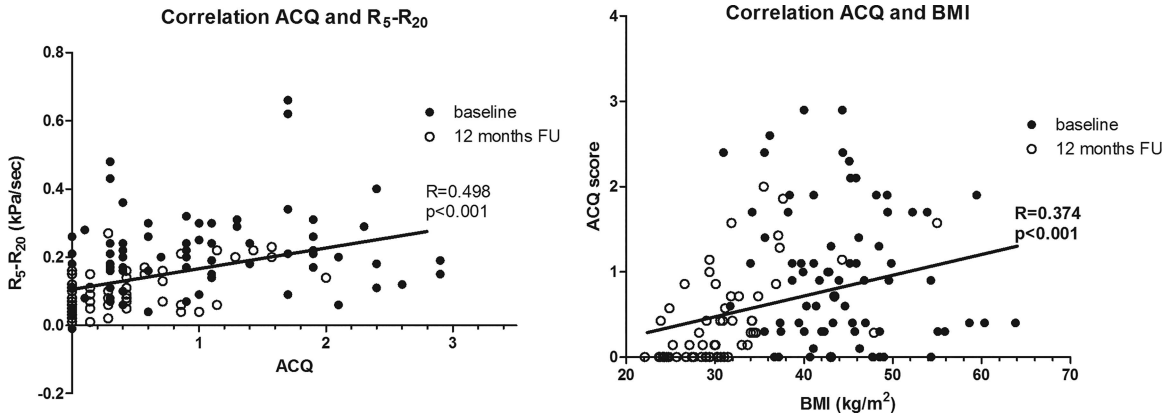

Figure 3 Correlation analysis of asthma control, small airway function and body mass index (BMI). Baseline data and 12-month follow-up data were used to calculate correlations. ACQ, Asthma Control Questionnaire.

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Table 3 Markers of systemic inflammation

	NBS+A				BS+A				BS−A			
	Baseline	6-month FU	12-month FU	p Value*	Baseline	6-month FU	12-month FU	p Value*	Baseline	6-month FU	12-month FU	p Value*
hs-CRP (ng/mL)	34.4 (1.3–142.0)	49.8 (20.0–142.0)	32.6 (8.5–142.0)	0.953	36.0 (4.3–142.0)	10.1 (1.8–75.6)	7.1 (0.8–139.5)	<0.001	30.4 (0.1–87.0)	13.8 (0.1–51.5)	5.3 (0.8–35.2)	<0.001
IL-6 (pg/mL)	0.7 (0.7–0.9)	0.7 (0.7–6.3)	0.7 (0.7–7.6)	0.655	0.7 (0.7–2.1)	0.7 (0.7–6.9)	0.7 (0.7–5.1)	0.211	0.7 (0.7–13.3)	0.7 (0.7–1.1)	0.7 (0.7–0.8)	0.017
IL-8 (pg/mL)	4.1 (3.0–6.6)	3.9 (1.9–7.3)	4.8 (1.8–8.7)	0.799	3.9 (2.7–13.5)	4.3 (2.4–10.0)	4.8 (1.2–13.3)	0.124	4.0 (1.9–9.1)	4.2 (0.7–7.5)	3.8 (2.1–7.8)	0.225
TNFα (pg/mL)	0.8 (0.8–0.8)	0.8 (0.8–2.8)	0.8 (0.8–2.9)	0.180	0.8 (0.8–1.3)	0.8 (0.8–3.0)	0.8 (0.8–2.4)	0.715	0.8 (0.8–1.0)	0.8 (0.8–1.5)	0.8 (0.8–0.8)	0.180
GM-CSF (pg/mL)	0.6 (0.6–1.7)	0.6 (0.6–26.8)	0.6 (0.6–9.4)	0.686	0.6 (0.6–3.9)	0.6 (0.6–11.5)	0.6 (0.6–3.5)	0.401	0.6 (0.6–0.6)	0.6 (0.6–0.9)	0.6 (0.6–1.5)	0.180
Adiponectin (ng/mL)	10.4 (7.0–17.7)	14.3 (5.9–246.9)	11.2 (5.7–235.6)	0.241	12.0 (4.5–22.0)	17.0 (8.8–1000.0)	22.5 (9.7–1000.0)	<0.001	14.1 (0.06–28.9)	17.6 (7.8–31.9)	23.3 (5.2–40.0)	<0.001
Leptin (ng/mL)	42 (2–97)	54 (4–100)	54 (3–86)	0.721	69 (18–100)	18 (2–98)	11 (0.2–69)	<0.001	55 (11–100)	7 (0.7–43)	6 (0.2–68)	<0.001

Data are presented as median (min–max).
*p Value for comparison baseline versus 12-month follow-up within each group (related samples Wilcoxon signed rank test).
BS+A, bariatric surgery and asthma group; BS−A, bariatric surgery without asthma group; FU, follow-up; GM-CSF, granulocyte macrophage colony-stimulating factor; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; NBS+A, no bariatric surgery and asthma group; TNF, tumour necrosis factor.

R_{20} in the BS+A group was significantly worse compared with the BS−A group, 12 months after bariatric surgery, there was no longer a significant difference between the two groups. This remained when only non-smokers were analysed (data not shown). Our data are in line with Al-Alwan *et al*,[16] who recently demonstrated that obese subjects with asthma have more collapsible peripheral airways than obese subjects without asthma, suggesting that altered lung mechanics play a role in the relationship between obesity and asthma. In addition to a correlation between R_5–R_{20} and BMI, we also found a correlation between R_5–R_{20} and ACQ, suggesting that increased R_5–R_{20} might explain the high symptom expression in obese subjects with asthma. Dixon *et al*[13] have shown previously that bariatric surgery was more beneficial to subjects with normal IgE levels (T_H2-low) in contrast to T_H2-high subjects, especially for small airway function.[18] In contrast, the present study could not find a relation between IgE levels and small airway function, and only found a relation in the high IgE group and bronchial hyperresponsiveness. Besides a difference in BMI between Dixon and our study (51 and 45 kg/m^2), the IgE level of our 'T_H2-high' group was higher, and the ratio of number of subjects in the low versus high group was different in our study compared with Dixon.

Whereas other studies have shown only a reduction in bronchial hyperreactivity 12 months after bariatric surgery,[13 15] in some of our patients the PD_{20} methacholine became negative, despite the decreased use of ICS in the 12-month follow-up. This was in contrast to the NBS+A subjects, in whom we did not succeed to taper off the ICS. Whether they truly needed ICS is questionable. We found a negative correlation between R_5–R_{20} and PD_{20}, suggesting that the increased peripheral airway resistance is associated with more severe bronchial hyperreactivity.

One hypothesis explaining the relationship between obesity and asthma is the concept of spill over of systemic inflammation caused by obesity, to the lungs, resulting in bronchial inflammation. Although others have demonstrated that obese subjects with asthma have more neutrophilic inflammation compared with lean subjects with asthma,[32 33] we have previously shown that there is no difference in neutrophil (or eosinophil) cell counts in bronchial biopsies between morbidly obese subjects with asthma and morbidly obese controls.[11] As we found no differences in cell counts at baseline, we expected no change in any cell count after bariatric surgery. However, our results demonstrate that in subjects with asthma, mast cell counts in bronchial biopsies taken 12 months after bariatric surgery decreased significantly compared with baseline. This decrease in mast cells might reflect a better asthma control. This decrease in mast cells could in part explain the improved asthma control, because mast cells contribute to inflammation and tissue remodelling in asthma. As the study was powered to detect changes in the primary endpoint FEV_1/FVC it could be that the number of patients investigated was not enough to detect subtle changes in bronchial inflammatory cells. Still none of the comparisons in cell counts showed a trend of being statistically different. Moreover, we found no differences in demographics between the group with follow-up bronchoscopy and those without (data not shown).

In line with previous reports,[34] we found that systemic inflammation (hs-CRP, leptin and adiponectin in serum) decreased after bariatric surgery. These data suggest that a reduction in systemic inflammation may result in reduction in local airway inflammation in subjects with asthma. However, the improvement after weight loss of especially the small airway

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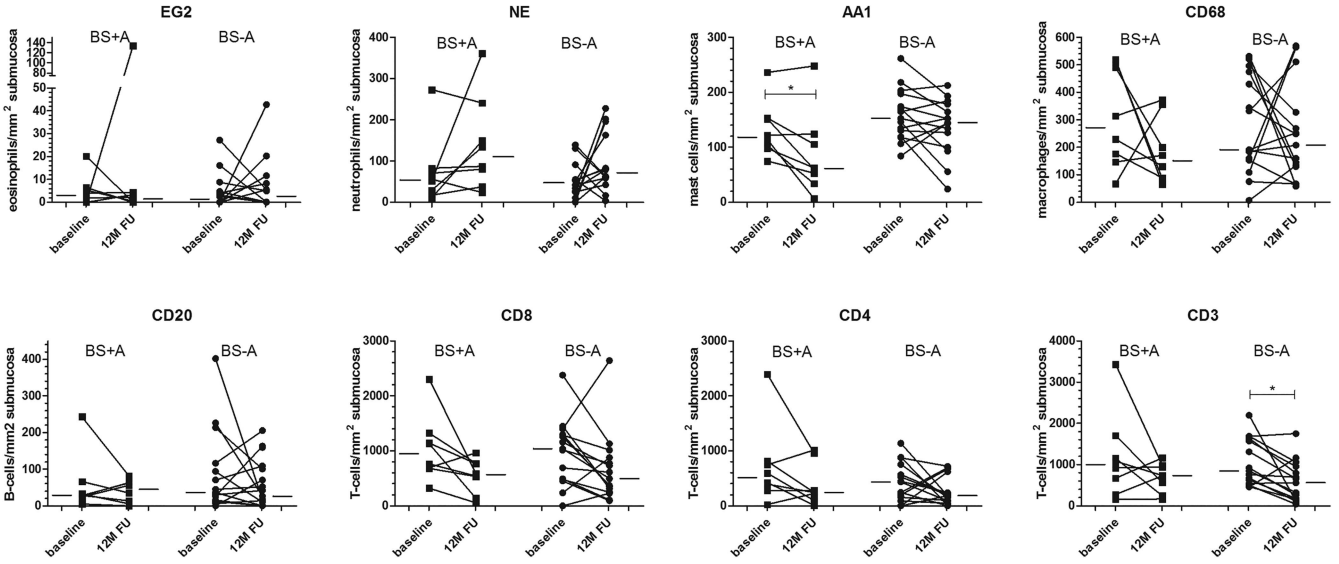

Figure 4 Submucosal cell counts of bronchial biopsies, before and 12 months after bariatric surgery. Bronchial submucosal cell count in morbidly obese subjects before and 12 months after bariatric surgery, with (BS+A, n=8, squares) and without asthma (BS−A, n=14, circles). p Values were calculated for the comparison between baseline and 12-month follow-up (12M FU) within each group, only significant p values are shown (*). Horizontal line represents median.

function, and the correlation between small airway function and ACQ reflects that bariatric surgery also improves the mechanical properties of the lungs. The observation that some obese patients develop asthma and other obese subjects do not has led to several hypotheses. Our data are in line with the suggestion made by Al-Alwan *et al*,[16] that obese subjects with asthma may be predisposed to the effect of obesity on small airways, which is supported by their data obtained by computational remodelling of airway wall stiffness and thickness, predicting a relationship between airway hyperresponsiveness and BMI.[35]

The strengths of our study are that we included an obese control group of subjects without asthma, as well as a control group of obese subjects with asthma without bariatric surgery. In addition, the group size in our study was larger than previous studies, and we not only performed data collection at 12 months but also at 3 and 6 months of follow-up. Furthermore, the diagnosis of asthma was performed strictly according to the GINA guidelines, as a doctor diagnosis of asthma in which symptoms play a major role has previously been shown to be not suitable for diagnosing asthma in patients with obesity.[19 36] Finally, participation was good and only few dropped out during the 12-month follow-up.

There are also some limitations to our study. First of all, we did not include a lean asthma group. Second, our obese asthma group without bariatric surgery is not fully comparable to both bariatric surgery groups due to differences in recruitment strategy. As a result, for example, the BMI is lower and this is because the frequency of patients with morbid obesity and asthma is low in our outpatient clinic. As a second bronchoscopy was optional, a bias is possible. Finally, bronchial biopsies were taken *centrally*, and therefore are not optimally suited to establish a possible relationship with *peripheral* airway function.

In summary, this is the first study that examined a wide variety of clinical, physiological, systemic and bronchial mucosal inflammatory parameters before and after bariatric surgery in morbidly obese subjects with asthma and morbidly obese control subjects. Although we found no improvement in our primary endpoint FEV_1/FVC, we did find improvement in asthma control, quality of life, medication use and PD_{20} methacholine. The significant improvement of R_5–R_{20} (peripheral airway function) after bariatric surgery, which was associated with BMI, ACQ and PD_{20}, suggests that peripheral airways play a major role in the relationship between obesity and asthma. Finally, bariatric surgery also decreased markers of systemic inflammation, and mast cell counts in central bronchial submucosa of obese subjects with asthma. Collectively these findings emphasise that weight loss as achieved by bariatric surgery should be a cornerstone in the treatment of morbidly obese patients with asthma. Further research regarding the role of small airways in obese asthma is needed.

Correction notice This article have been corrected since it was published Online First. The '*Provenance and peer review*' has been corrected.

Acknowledgements We wish to thank Mr Erwin Birnie for statistical advice, and Miss Vera van Rijn and Mrs Annemarie van Schadewijk for their help with the analysis of the bronchial biopsies and systemic inflammation. We are grateful for the help of all pulmonologists, the staff in the Respiratory Laboratory, Department of Clinical Chemistry, and surgeons, anaesthetists and other members of the Bariatric Surgery Team at the Sint Franciscus Gasthuis.

Collaborators Annemarie van Schadewijk.

Contributors Conception and design: AvH, AR, MCC, CT, PH, G-JB. Analysis and interpretation: AvH, G-JvdG, CT, PH, G-JB, AvS. Drafting of the manuscript for important intellectual content: AvH, AR, MCC, LB, G-JvdG, CT, PH, G-JB. Guarantor: AvH, CT, PH, G-JB.

Funding This research was supported by grants from Foundation Research and Development Department of Internal Medicine Sint Franciscus Gasthuis (Stichting Onderzoek en Ontwikkeling Interne Specialismen Sint Franciscus Gasthuis).

Competing interests None.

Patient consent Obtained.

Ethics approval Toetsingscommissie Wetenschappenlijk Onderzoek Rotterdam e.o.

Provenance and peer review Not commissioned; externally peer reviewed.

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Effect of bariatric surgery on asthma control, lung function and bronchial and systemic inflammation in morbidly obese subjects with asthma

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Thorax 2015 70: 659-667 originally published online April 30, 2015
doi: 10.1136/thoraxjnl-2014-206712

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Supplementary material

Methods

The subjects included in this study were patients who underwent pre-operative screening before bariatric surgery in the Sint Franciscus Gasthuis in Rotterdam, the Netherlands from September 2009 to April 2011. Eligibility criteria for bariatric surgery were: age between 18 and 60 years old, body mass index (BMI) $\geq$ 35 kg/m^2. We excluded people who (a) were older than 50 years of age or; (b) had a history of smoking more than 10 cigarettes a day, or were currently smoking more than 10 cigarettes a day (with the aim to decrease the risk of including subjects with chronic obstructive pulmonary disease [COPD]); (c) were taking oral corticosteroid therapy; (d) had an asthma exacerbation four weeks before screening; (e) were unable to perform pulmonary function tests; or (f) had pulmonary disease other than asthma.

All subjects underwent baseline physical examinations including routine assessment of anthropometry and blood pressure and collection of blood samples. Waist circumference was measured directly to the body surface midway between the lower rib margin and the ileac crest. Fat free mass and fat weight (in kg and % body weight) were measured using bio-electrical impedance analysis (Bodystat 1500, Bodystat Ltd, British Isles).

Percentage excess weight loss (%EWL) was calculated as: (BMI baseline – BMI 12 months follow up) / (BMI baseline – 25) * 100.

Pulmonary function tests

Spirometry was performed with Vmax spirometer (Vmax SensorMedics Viasys, type Encore 20/22/229/62 Encore, Cardinal Health, USA) before and after 400 µg of inhaled salbutamol, according to the American Thoracic Society / European Respiratory Society guidelines[20, 21]. Static lung volumes were measured by body plethysmography, directly after the spirometry. If applicable, subjects were asked not to use longacting β2-agonists for 48 h, short-acting β2-agonists for 8 h and anti-histamines or anti-leukotriene medication 72 h before lung function

testing. Subjects who were using inhaled corticosteroids (ICS), were asked to discontinue them until bariatric surgery. Daily symptom diary and daily peak flow rates were used to screen asthma control. Subjects were permitted to use short-acting bronchodilators as rescue medication. After six weeks they returned for their second visit, during which exhaled Nitric Oxide (FeNO)(Niox mino Aerocrine, Sweden)[22], impulse oscillometry (IOS) (Masterscreen IOS system, Erich Jaeger Co., Würzburg, Germany), diffusion capacity (intrabreath method, corrected for hemoglobin and alveolar volume)[23] and methacholine provocation testing (five breath dosimeter method)[24, 25] were performed. Bronchial responsiveness to methacholine was expressed as the provocative dose of methacholine inducing a 20% fall in FEV_1 (PD_{20}). A PD_{20} < 1.8 mg was considered as a positive provocation test. If the methacholine provocation test was negative, a second provocation test was performed six weeks later. If the methacholine provocation test was negative, a second provocation test was performed six weeks later. The use of ICS was allowed during follow up.

At 3 and 6 month follow-up FEV_1 was measured by methacholine provocation testing. At 12-month follow-up two visits were scheduled. During the first visit, spirometry and body plethysmography were performed. During the second visit, Fe_{NO}, IOS, diffusion capacity and methacholine provocation testing were performed.

Questionnaires and comorbidities

Based on questionnaires the subjects with asthma were grouped into child onset of asthma if they have had the diagnosis asthma before the age of 18, and adult onset of asthma from 18 years or older. Asthma symptoms were assessed by the mini Asthma Quality of Life Questionnaire (AQLQ)[26] and the Asthma Control Questionnaire (ACQ)[27] to assess asthma complaints. An delta of 0.5 in either AQLQ or ACQ was considered clinically significant. The Epworth Sleepiness Scale[28] questionnaire was used to assess OSAS, and the GERD-Questionnaire for gastro-esophageal reflux disease (GERD)[29]. The average of 7 days data

collected with an activity meter was used to determine the total number of steps taken a day, as a measure of activity. Metabolic syndrome was diagnosed according to the National Cholesterol Education Program's Adult Treatment Panel III report (NCEP ATP-III) criteria when ≥3 of the following 5 risk factors were present: abdominal obesity, an elevated level of serum triglycerides, low serum level of high-density lipoprotein cholesterol (HDL-C), elevated blood pressure, and high serum glucose level or treatment for any of these disorders[30].

Atopy

Atopy was defined as either a positive skin-prick test (SPT) or a positive serum inhalation screen. The skin-prick tests (SPT) consisted of a battery of common aeroallergens: house-dust mite; dog, cat, and horse dander; *Aspergillus fumigatus*; mugwort; and birch and grass pollen (Vivodiagnost; ALK Benelux BV, Groningen, The Netherlands). A positive SPT was defined as at least one reaction to the aforementioned allergens as compared to the histamine positive control and saline solution-negative control. Total IgE and specific serum IgE were determined with a solid-phase two-step chemiluminescent immunoassay on the Immulite 2000 (Siemens, Los Angeles, CA). A positive serum inhalation screen was defined as at least one increased amount of specific IgE for fungus, house-dust mite, cat, dog, grass, birch or herbs.

Laboratory

Laboratory measurements were performed according to standard procedures by our Department of Clinical Chemistry. Plasma-cholesterol, HDL-cholesterol, glucose, and triglycerides, were measured using LX-20 and DxC analyzers (Beckman Coulter, Miami, FL, USA). LDL-cholesterol was calculated using the Friedewald formula. Blood cell counts and 5-part leukocyte differentiation were determined automatically using LH750 or DxH800 analyzers (Beckman Coulter). Vitamin D was determined by radioimmunoassay or chemiluminescence (LIA) on Liason analyzers (DiaSorin, Stillwater, MN, USA). Serum

markers of systemic inflammation were assessed using the Meso Scale Discovery Platform (Meso Scale Discovery, Gaitherburg, MD), for IL-6, IL-8, high-sensitivity (hs)-CRP, TNFα, GM-CSF, leptin and adiponectin. Lower limit or upper limit of detection were respectively 0.7-2500 pg/ml, 0.6-2500 pg/ml, 0.05-142 ng/ml, 0.8-2500 pg/ml, 0.61-2500 pg/ml, 0.2-100 ng/ml and 0.064-1000 ng/ml. All values which were below or above the lower or upper limit of detection of the assay, were arbitrarily set at these limits.

Results

In the BS+A group median BMI decreased from 45.1 kg/m^2 to 35.9 kg/m^2 at 3-month follow-up, 33.0 kg/m^2 at 6-month follow-up and 30.2 kg/m^2 at 12-month follow-up ($p<0.001$ for all comparisons). In the BS-A group median BMI decreased from 43.1 kg/m^2 to 36.0 kg/m^2 at 3-month follow-up, 32.3 kg/m^2 at 6-month follow-up and 29.0 kg/m^2 at 12-months follow-up ($p<0.001$ for all comparisons). The BMI was stable in the NBS+A group (35.6 kg/m^2 at baseline, 35.3 kg/m^2 at 3-month follow-up, 35.6 kg/m^2 at 6-month follow-up and 36.2 kg/m^2 at 12-month follow-up).

Also the median abdominal circumference improved in the BS+A group (133 cm baseline, 99cm 12-month follow-up; $p<0.001$) as well as in the BS-A group (127 cm baseline, 93 cm 12-month follow-up; $p<0.001$), but not in the NBS+A group (119 cm baseline, 113 cm 12-month follow-up).

AQLQ improved clinically and statistically significantly at 12-month follow-up as compared to baseline for the BS+A group (median 5.6 to 6.7, $p= 0.002$), and BS-A group (median 6.3 to 6.9, $p<0.001$). There was no significant improvement in the NBS+A group (median 5.5 to 5.8, $p=0.075$). ACQ improved clinically and statistically significantly at 12-month follow-up as compared to baseline for BS+A group (median 1.2 to 0.4, $p= 0.001$), and the NBS+A group (1.7 to 1.0, $p= 0.012$), and only statistically significantly in the BS-A group (median 0.3 to 0.0, $p= 0.001$). While there was a significant difference between BS+A and BS-A group at

baseline (p=0.001), there was no difference between these group at 12-month follow-up

(p=0.057).

Table S1 B Demographics of the study population

	NBS+A	BS+A	BS-A	p Value
Bio-impedance				
Fat free Mass	56.3 (42.9-7-9)	61.2 (47.8-100.5)	62.0 (47.2-74.7)	0.103
Fat weight (%)	43.5 (24.5-59.5)	50.9 (37.6-70.4)	50.6 (31.1-59.1)	0.124
Fat weight (kg)	45.1 (27.6-79.0)	68.1 (44.5-134.4)	62.3 (32.0-100.0)	0.046
Asthma				
Medication use at inclusion study				
Short acting bronchodilator	35.7%	41.4%	25.0%	0.367
Long acting bronchodilator	14.3%	3.4%	2.3%	0.153
Antileukotrienes	35.7%	0%	2.3%	<0.001
B_2 sympaticomimetica/ ICS	71.4%	20.7%	6.8%	<0.001
Inhaled corticosteroids	21.4%	17.2%	6.8%	0.227
Antihistamines	23.1%	24.1%	13.6%	0.447
Nasal corticosteroids	71.4%	17.2%	11.4%	<0.001

Age of onset of asthma (% as child)	75%	33%		
Atopy				
Positive inhalation screen	Not done	69.2%	42.4%	0.049
Skin prick test (% ≥1 positive wheal)	78.6%	55.2%	31.8%	0.005
IgE (kU/L)	90.7 (5.8-2026.0)	213 (5.0-2329)	52 (1.4-761.0)	0.041
Comorbidities				
Epworth Sleepiness Scale	2 (0-16)	2 (0-8)	2 (0-9)	0.964
GERD-questionnaire	6 (4-12)	6 (4-12)	6 (2-14)	0.296
Steps a day	7191 (3307-9587)	4964 (2021-12176)	4613 (2061-10083)	0.155
Metabolic syndrome	27.3%	59.3%	53.8%	0.206
Laboratory[1]				
Cholesterol (mmol/L)	4.3 (2.9-5.8)	4.7 (3.4-7.4)	5.0 (3.0-6.9)	0.570
HDL-cholesterol (mmol/L)	1.1 (0.8-1.7)	1.1 (0.7-2.3)	1.2 (0.7-2.1)	0.725
LDL-cholesterol (mmol/L)	2.7 (1.0-3.6)	2.9 (1.8-5.1)	3.0 (1.6-4.8)	0.634

Triglyceride (mmol/L)	1.2 (0.8-2.4)	1.7 (0.6-3.3)	1.4 (0.5-5.1)	0.080
Glucose (mmol/L)	5.2 (4.2-9.4)	5.6 (4.6-9.5)	5.9 (4.0-27.1)	0.029
Peripheral blood count				
Leukocytes (10^9 /L)	9.2 (4.6-12.3)	8.7 (5.3-13.1)	7.2 (4.6-11.9)	0.057
Neutrophils (%)	59 (37-79)	61 (45-72)	59 (46-70)	0.144
Lymphocytes (%)	31 (15-48)	28 (15-45)	31 (20-47)	0.282
Monocytes (%)	7 (4-14)	7 (5-13)	6 (4-13)	0.837
Eosinophils (%)	2 (0-7)	2 (0-9)	2 (0-6)	0.965
Basophils (%)	0 (0-1)	0 (0-1)	0 (0-2)	0.814

Data are presented as median (min-max).
[1] non fasting blood

BS+A,bariatric surgery and asthma group; BS-A, bariatric surgery without asthma group; ICS, inhaled corticosteroid; NBS+A, no bariatric surgery and asthma group.

Table S4 Submucosal cell counts of bronchial biopsies, before and 12 months after bariatric surgery

	BS+A			**BS-A**		
	Baseline	**12-month FU**	**p Value**	**Baseline**	**12-month FU**	**p Value**
Eosinophils (EG2)	3.0 (0.04-20.2)	1.4 (0.04-133.2)	0.889	1.3 (0.03-27.1)	2.5 (0.04-42.7)	0.826
Neutrophils (NE)	54 (11-273)	111 (24-361)	0.208	47 (0.1-139)	71 (3-228)	0.221
Mast cells (AA1)	118 (75-236)	61 (6-248)	0.036	152 (84-262)	145 (24-213)	0.125
Macrophages (CD68)	271 (67-520)	151 (65-373)	0.161	191 (7-531)	208 (58-569)	0.570
B cells (CD20)	28 (5-243)	45 (0.1-82)	1.000	36 (0.1-402)	26 (0.1-205)	0.570
T cells (CD8)	945 (321-2304)	566 (55-965)	0.050	1040 (0.2-2377)	493 (94-2641)	0.053
T cells (CD4)	510 (24-2393)	241 (6-1013)	0.161	434 (0.07-1136)	186 (0.04-719)	0.211
T cells (CD3)	1000 (161-3433)	732 (164-1165)	0.401	844 (459-2193)	559 (43-1753)	0.015

Bronchial submucosal cell count in morbidly obese subjects before and 12 months after bariatric surgery, with (BS+A, n=8) and without asthma (BS-A, n=14). p Values were calculated for the comparison between baseline and 12 months follow up within each group. Data are presented as the median (min-max), cells/mm^2 submucosa.