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Predictors of a good response to inhaled corticosteroids in obesity-associated asthma

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ABSTRACT

Introduction: Asthma in obese subjects is poorly understood. According to GINA guidelines, pulmonologists increase ICS in case of poor asthma control but lung volume restriction may also worsen respiratory symptoms in obese asthmatics leading to overtreatment in this subpopulation.

Methods: We conducted a retrospective study on 1217 asthmatics recruited from University Hospital of Liege. 92 patients with a BMI ≥30 came at least two times at the asthma clinic (mean interval: 335 days). In this obese population, we identified predictors of good (decrease in ACQ ≥0.5) versus poor response (rise in ACQ ≥0.5) to ICS step-up therapy.

Results: Obese asthmatics had a poorer asthma control and quality of life as compared to non-obese and exhibited reduced FVC, higher levels of blood leucocytes and markers of systemic inflammation. The proportion of asthma inflammatory phenotypes was similar to that observed in a general population of asthmatics. Among uncontrolled obese asthmatics receiving ICS step-up therapy, 53% improved their asthma control while 31% had a worsening of their asthma. Uncontrolled obese asthmatics showing a good response to increase in ICS had higher ACQ, lower CRP levels, higher sputum eosinophil counts and higher FeNO levels at visit 1. Uncontrolled obese asthmatics that worsened after increasing the dose of ICS had lower FVC, lower sputum eosinophil counts and higher sputum neutrophil counts.

Conclusion: We observed poorer asthma control in obese asthmatics despite similar bronchial inflammation. Managing obese asthmatics according to ACQ alone seems to underestimate asthma control and the contribution of restriction to dyspnea. Increasing the dose of ICS in the absence of sputum eosinophilic inflammation or in the presence of restriction or bronchial neutrophilia led to poorer asthma control. In those patients, management of obesity should be the first choice.

1. Introduction

Asthma in obese subjects is poorly understood. Asthma and obesity are both common diseases in developed countries. More than 600 million people are obese worldwide. According to the data from our asthma clinic, 20% of our asthmatics are obese and this rate increases up to 25% in severe asthmatics included in the Belgian Severe Asthma Registry [1]. The majority of studies evaluating the link between obesity and the prevalence and incidence of asthma in adults or exploring the relationship between obesity and asthma severity concluded that obesity was associated with a significant increase in the annual risk of a new diagnosis of asthma [2–4]. The association of obesity with severe asthma remains controversial. It has been suggested that obesity was a consequence of asthma treatment but it is now clear that obesity often precedes asthma [5]. Mechanical [6], inflammatory and genetic factors [7] contribute to the development of asthma in obese patients [8].

The aim of asthma management is to obtain asthma control and to reduce the risk of exacerbation. The GINA guidelines [9] recommend to step-up or step-down the ICS dose according to asthma symptoms questionnaires. However, obese patients do not respond as well as normal-weight individuals to inhaled corticosteroids or inhaled corticosteroid/long-acting bronchodilator combination medications [10,11] Obesity indeed causes physiologic impairment in lung function due to the mechanical effect of central body fat distribution [12] and symptoms related to lung volume restriction will not improve with a step-up of asthma therapy. This could lead to obese asthma overtreatment. In

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the area of personalized medicine, the obese-asthma phenotype remains controversial [13–16], some of the clusters analysis suggesting that this obese asthma phenotype is not a uniform group and identifying two major subgroups according to TH_2 inflammation and the age of onset.

The aim of this study was to describe the characteristics of obese as compared to normal-weight asthmatics and to identify predictors of poor or good responders to ICS step-up therapy in this particular asthmatic population.

2. Material and methods

2.1. Subject characteristics

We conducted a retrospective study on a series of 1217 patients with asthma recruited from the University Asthma Clinic of Liege between October 2005 and June 2017. The patients came from routine practice to University Hospital and were recruited by two clinicians involved in asthma. Entry criteria were any patients with asthma aged 18yrs or more who accepted to undergo detailed investigation at the Asthma Clinic. The visits were not parts of an asthma trial. All the patients that had a successful sputum induction were included in the study. Their demographic and functional characteristics are summarised in Tables 1 and 2.

Asthma was diagnosed based on the presence of chronic respiratory symptoms such as cough, breathlessness or dyspnoea together with the demonstration of airflow variability. The latter was defined by airway hyper-responsiveness shown by one or more of the following: increase in Forced Expiratory Volume in 1 s (FEV_1) of > 12% and 200 ml following inhalation of 400 µg salbutamol (VENTOLIN™, GSK Belgium) or inhaled concentration of methacholine (Methapharm inc., Brandford, Ontario, Canada) provoking a 20% fall in FEV_1 of < 16 mg/ml. Methacholine challenge was performed according to a standardised methodology as previously described [17]. Subjects were characterised as atopic if they had at least one positive specific IgE (> 0.35kU/l; Phadia) for at least one common aeroallergen (cat, dog, house dust mites, grass pollen, tree pollen and a mixture of moulds). Patients with a smoking history of more than 20 pack-years were excluded. Subjects with BMI under 30 were defined as non-obese and subjects with BMI over 30 as obese asthmatics.

2.2. Study design

Patients underwent FeNO measurement at a flow rate of 50 ml/s according to the ERS/ATS recommendations (NIOX, Aerocrine, Sweden). FeNO was first measured and followed by spirometry with bronchodilation, sputum induction and blood sampling. All tests were performed on the same day.

Quality of life was assessed using the self-administered Asthma Quality of Life Questionnaire (AQLQ [18]) and asthma control by the Juniper Asthma Control Questionnaire (ACQ [19]). Sputum was induced and processed as previously reported [20]. Cell count were estimated on samples centrifuged (Cytospin) and stained with Diff Quick after counting 500 cells (Dade, Brussels, Belgium).

2.3. Statistical analyses

The results were expressed as means ± standard deviation (SD) for continuous variables or as medians and interquartile ranges (IQR) for skewed distributions. For categorical variables, the number of observations and percentages were given in each category. Comparisons between different subgroups were performed with ANOVA test or a Kruskal-Wallis test. The Spearman correlation coefficient was used to measure the association between clinical parameters. Univariate linear regression models were used to assess the relationship between ACQ, AQLQ and BMI with a set of covariates. Some parameters were log-transformed to normalize their distribution. ICS was divided in three groups according to tertiles (< 400, ≥400-1000, ≥1000). A multivariate analysis with stepwise selection was done including all independent variables. The results were considered to be significant at the 5% critical level ($p < 0.05$). Calculations were done using SAS Version 9.1 (SAS Institute, Cary, North Carolina, USA).

Table 1
Demographic and clinical characteristics of asthmatics classified according to BMI.

	Overall	BMI < 30	BMI 30–35	BMI ≥ 35
N	1217	969 (80%)	177 (14%)	71 (6%)
Sex (F)	717 (59%)	565 (58%)	103 (58%)	49 (69%)
Age, years	49 (35–60) ****	47 (33–60)	54 (43–64) ††††	50 (37–62)
Smoking history (S/ES/NS), %	21/26/53	22/26/52	19/31/50	17/23/60
Packs-years	0 (0–10)	0 (0–8)	0 (0–17)	0 (0–7)
Atopy (Y)	706 (58%)	610 (63%)	97 (55%)	36 (51%)
Exacerbation (n/yr)	0.66	0.68	0.48	0.67
ICS	766 (63%)	594 (61%)	114 (64%)	55 (77%) ∞
Beclomethasone equivalents	400 (0–1000) **	400 (0–1000)	800 (0–1000)	800 (200–2000) ∞ ∞
OCS	87 (7%)	65 (7%)	14 (8%)	8 (11%)
LABA	711 (58%)	541 (56%)	116 (66%) †	54 (76%) ∞ ∞
LTRA	292 (24%)	222 (23%)	44 (25%)	26 (37%) ∞
Anticholinergics	352 (29%)	267 (28%)	57 (32%)	28 (39%)
FEV_1%	84 ± 21	84 ± 21	83 ± 22	80 ± 21
FVC%	95 ± 18 **	96 ± 18	92 ± 21	89 ± 19 ∞ ∞
FEV_1/FVC	73 ± 11 **	73 ± 11	75 ± 11	76 ± 10∞
ACQ	2,01 ± 1,23 ****	1,93 ± 1,22	2,28 ± 1,21 ††	2,51 ± 1,21 ∞ ∞ ∞
ACT	15 ± 5 ****	15 ± 5	14 ± 5 †	12 ± 5 ∞ ∞ ∞
AQLQ	4,52 ± 1,36 ****	4,61 ± 1,34	4,25 ± 1,31 ††	3,84 ± 1,48 ∞ ∞ ∞ ∞
Age of onset	30 (11–50)	31 (12–49)	32 (12–84)	28 (10–51)
Early/late onset (< 12/ > 40 yr)	258/391	204/310	40/58	14/23

† compares BMI 30–35 to BMI < 30 group; ∞ compares BMI ≥ 35 to BMI < 30 groups; ^{x} compares BMI ≥ 35 to BMI 30–35 groups. */†/∞/^{x}: p < 0,05. **/††/∞ ∞/^{x} ^{x}:p < 0,01. ***/†††/∞ ∞ ∞/^{x} ^{x} ^{x}: p < 0,001. ****/††††/∞ ∞ ∞ ∞/^{x} ^{x} ^{x} ^{x}: P < 0,0001.

BMI: body mass index. F: female. M: male. S: current smoker. ES: ex-smoker. NS: non-smoker. Y: yes. N/yr: number per year. ICS: inhaled corticosteroids. OCS: oral corticosteroids. LABA: Long acting Beta 2 Agonists. LTRA: leukotriens receptor antagonists. FEV_1: forced expiratory volume in one second. FVC: forced vital capacity. ACQ: asthma control questionnaire. ACT: asthma control test. AQLQ: asthma quality of life questionnaire.

Table 2
Inflammatory characteristics of asthmatics classified according to BMI.

	Overall	BMI < 30	BMI 30–35	BMI ≥ 35
Blood leucocytes, 10^6/mm^3	7,5 (6,2–9,1) ***	7,3 (6,1–8,9)	7,8 (6,7–9,4) †	8,2 (6,8–9,7) ∞
Blood neutrophils, 10^3/mm^3	4059 (3156–5392) **	3970 (3061–5325)	4237 (3465–5607)	4482 (3685–5824)
Blood lymphocytes, 10^3/mm^3	2328 (1869–2848) ****	2270 (1850–2771)	2558 (2035–3165) †††	2528 (2002–3212) ∞
Blood eosinophils, 10^3/mm^3	190 (110–333)	191 (110–335)	181 (109–320)	184 (109–350)
Blood monocytes, 10^3/mm^3	511 (397–668) **	500 (388–657)	514 (424–672)	563 (465–725) ∞
Blood basophils, 10^3/mm^3	36 (24–53)	36 (23–53)	37 (27–57)	36 (23–54)
Blood neutrophils, %	56 (49–62)	56 (49–62)	56 (50–62)	57 (48–64)
Blood lymphocytes, %	32 (26–38)	32 (26–38)	33 (27–39)	31 (24–39)
Blood eosinophils, %	2,6 (1,5–4,3)	2,7 (1,5–4,5)	2,4 (1,6–4)	2,6 (1–4)
Blood monocytes, %	6,9 (5,4–8,5)	6,9 (5,4–8,6)	6,7 (5,4–8,4)	7,2 (5,7–8,8)
Blood basophils, %	0,5 (0,3–0,7)	0,5 (0,3–0,7)	0,5 (0,3–0,7)	0,4 (0,3–0,6)
CRP, mg/L	2,4 (1–6) ****	2 (0,9–6)	3,3 (2–6) ††††	4,4 (2.1–9,4) ∞ ∞ ∞
Fibrinogen, g/L	3,2 (2,8–3,7) ****	3,2 (2,7–3,6)	3,5 (2,9–3,9) ††	3,7 (3,2–4,2) ∞ ∞ ∞ ∞
IgE, kU/L	120 (39–335)	123 (40–349)	118 (41–302)	84 (34–269)
Total cell count (10^6/g)	1042 (311–3027)	1150 (241–3658)	1025 (188–2925)	1231 (481–3606)
IS eosinophils, 10^3/mm^3	21 (0,5–173)	21 (0–176)	20 (1,9–138)	25 (0,5–192)
IS neutrophils, 10^3/mm^3	474 (160–1556)	460 (156–1482)	548 (195–1849)	714 (198–2295) ∞
IS lymphocytes, 10^3/mm^3	14,6 (3,1–45,4)	13,8 (2,9–43,9)	16,4 (3–46,8)	19,7 (7,7–57,7)
IS macrophages, 10^3/mm^3	262 (111–640)	258 (106–643)	257 (112–604)	345 (159–802)
IS eosinophils, %	1,8 (0,2–10,8)	1,8 (0,2–11)	1,6 (0,3–9,4)	1,8 (0,2–10,8)
IS neutrophils, %	51,4 (27,4–75,3)	51 (26,6–76)	53,5 (32,9–72,4)	51,5 (27,6–75,2)
IS lymphocytes, %	1,4 (0,5–2,7)	1,2 (0,4–2,8)	1,6 (0,5–2,6)	1,6 (0,7–2,6)
IS macrophages, %	23,8 (11,1–44,3)	23,8 (10,6–45,6)	23 (12,2–39,9)	26,4 (13–45)
FeNO, ppb	24 (14–49) **	25 (14–52)	20 (12–42) †	22 (12–35)

*Global p-value; † compares BMI 30–35 to BMI < 30 group; ∞ compares BMI ≥ 35 to BMI < 30 groups; ^{x} compares BMI ≥ 35 to BMI 30–35 groups. */†/ ∞/ ^{x}: p < 0,05. **/††/ ∞ ∞/ ^{x} ^{x}:p < 0,01. ***/†††/ ∞ ∞ ∞/ ^{x} ^{x} ^{x}: p < 0,001. ****/††††/ ∞ ∞ ∞ ∞/ ^{x} ^{x} ^{x} ^{x}: P < 0,0001.
CRP: C reactive protein. IgE: immunoglobulin E. IS: induced sputum. FeNO: fractional exhaled nitric oxide. Ppb: part per billion.

3. Results

3.1. Baseline characteristics

Complete assessment was obtained in 1217 subjects with physician-diagnosed asthma. 20% of our general asthmatic population was obese and 6% had a BMI ≥35. Female was the predominant gender and mean age of our asthmatics was 49 years old with obese patients tending to be older (Table 1). 21% were current smokers while 26% were ex-smokers. Atopy did not differ according to BMI. Obese asthmatics received higher doses of ICS and more frequently LABA and anti-leukotrienes than non-obese. Overweight patients had poorer asthma control and quality of life. 72% of our obese asthmatic population had uncontrolled asthma. When looking more in depth at the ACQ questionnaire, it appeared that obese patients had significantly more morning symptoms, activity limitation, breathlessness and short-acting bronchodilator use than non-obese (p < 0.05). They did not report more frequent nocturnal awakening or wheezing. Asthmatics with a BMI ≥30 had similar FEV_1 values but reduced FVC (Table 1). Early onset of asthma was observed in one fifth of asthmatics while one third of the cohort had onset of disease after the age of 40 years old and this was similar within the different BMI subgroups.

Absolute value of blood leucocytes, including neutrophils, lymphocytes and monocytes were correlated with BMI with obese patients showing the highest levels (Table 2). CRP and Fibrinogen levels also increased with BMI. Successful sputum was obtained in 83% of the asthmatic population. The proportion of airway inflammatory phenotypes was similar in different weight subgroups (Fig. 1) but we found a significant increase in absolute sputum neutrophil counts in obese patients. Obese did not exhibit higher rate of exacerbations.

3.2. Independent factors of poor asthma control and quality of life

We conducted a multiple regression analysis in the general population of asthmatics to highlight independent predictors of asthma control (Table 3). Higher BMI, tobacco smoking, sputum eosinophil counts and high ICS dose were predictors of poorer asthma control

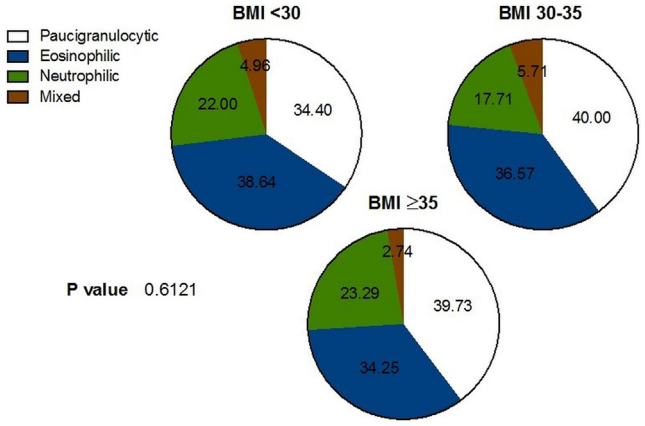

Fig. 1. Proportions of airway inflammatory phenotypes in asthmatics classified according to BMI.

while higher FEV_1 values were associated with better asthma control (r^2 = 0.40, p < 0.0001). As for quality of life, multiple logistic regression analysis showed that male gender and higher FVC were independent predictors of better asthma quality of life while higher BMI and high doses ICS were associated with poorer AQLQ (r^2:0.23, p < 0.0001).

3.3. Effect of ICS in obese asthmatics

Among the 146 uncontrolled asthmatics with normal weight that were prescribed an ICS step-up therapy, 88 patients (60%) had an improvement of their asthma control at the following visit (decrease in ACQ ≥0.5) while 33 patients (23%) had a worsening of their asthma (increase ≥0.5 in ACQ score, Table 4). In the obese asthma population where ICS step-up therapy was prescribed due to poor asthma control (n = 57), 29 asthmatics (53%) improved their asthma control while 17 patients (31%) had a worsening of their asthma symptoms (Table 4). The rate of responders did not significantly differ between obese and normal-weight asthmatics (p > 0.05).

Table 3
Univariate and multivariate linear regression models to assess the relationship between Asthma control questionnaire (ACQ) and a set of covariates.

ACQ	UNIVARIATE		MULTIVARIABLE With stepwise selection	
	Univariate Estimate (SE)	P-value	Estimate (SE)	P-value
Tobacco Current Ex-smokers	0.57 (0.090)	< 0.0001	0.56 (0.085)	< 0.0001
	0.16 (0.083)			
BMI	0.036 (0.0071)	< 0.0001	0.027 (0.0071)	0.0002
FEV_1	−0.033 (0.0014)	< 0.0001	−0.029	< 0.0001
FVC	−0.033 (0.0019)	< 0.0001		
FEV_1/FVC	−0.036 (0.003)	< 0.0001		
ICS		< 0.0001		
400–1000	0.40 (0.084)		0.40 (0.086)	< 0.0001
> 1000	0.91 (0.079)		0.75 (0.084)	< 0.0001
Ln Leucocytes	1.10 (0.12)	< 0.0001		
Ln Lympho %	−0.69 (0.11)	< 0.0001		
Ln Blood Eosinophils (/μL)	0.18 (0.041)	< 0.0001		
Ln Blood Neutrophils (/μL)	0.73 (0.085)	< 0.0001		
Ln Basophils (/μL)	0.28 (0.059)	< 0.0001		
Ln Fibrinogen	0.35 (0.18)	0.046		
Ln CRP	0.17 (0.034)	< 0.0001		
Ln Sputum Macrophages	−0.23 (0.035)	< 0.0001		
Ln Sputum Eosinophils	0.13 (0.023)	< 0.0001		
Ln Sputum Lympho, AV	0.087 (0.025)	0.0004		
Ln Sputum Neutrophils, AV	0.090 (0.02)	< 0.0001		
Ln Sputum Eosinophils, AV	0.12 (0.018)	< 0.0001	0.095	< 0.0001

Independent variables included were age, forced expiratory volume in one second (FEV_1), Forced vital capacity (FVC), FEV_1/FVC, Asthma control test (ACT), Asthma quality of life questionnaire (AQLQ), Body mass index (BMI), tobacco smoking (non-smokers – ex-smokers – current smokers) and pack-years, and were log-transformed for FeNO, blood leucocytes, fibrinogen, CRP, IgE and induced sputum cell counts. Inhaled corticosteroids (ICS) was divided in three groups according to tertiles (< 400, ≥400-1000, ≥1000). Significant variables in the univariate model are reported in the table. A multivariate analysis with stepwise selection was done including all significant variables from the univariate model.

Uncontrolled obese asthmatics showing a good response to increase in ICS dose had poorer baseline ACQ (3.27 ± 1.22 vs 2.24 ± 1.11, p < 0.01), lower CRP levels (2.9 (0.9–5.2) vs 5 (3.2–8.8), p = 0.04), higher sputum eosinophil counts either taken in percentage (23.6% (3.1–50) vs 6.2% (0.6–15), p = 0.01) or in absolute value (393 (35–1170) vs 72 (2–274), p = 0,02) and higher FENO levels (48 (20–74) vs 18 (12–43), p = 0.01). Uncontrolled obese asthmatics who worsened their asthma after increasing the dose of ICS had lower FVC (78% ± 19% vs 91% ± 17%, p = 0.04), lower sputum eosinophil counts (1.4% (0.6 – 9.8) vs 11% (1.8–29), p = 0.03) and higher sputum neutrophil counts (73.4% (58–90) vs 43.4% (16–71), p = 0.04). After exclusion of current smokers, we found exactly the same characteristics of good and poor response to ICS. We did not find any differences in treatment response when looking at the age of onset.

4. Discussion

Obese asthmatics represent 20% of our asthmatic population. Obesity is associated with poor asthma control and quality of life and obese asthmatics exhibit signs of systemic inflammation.

We found that obese asthmatics have the same predictors of response to ICS than non-obese. The "obesity-associated asthma" phenotype includes a subgroup of patients with eosinophilic inflammation who will show a good response to ICS and another subgroup who is characterized by low FVC and neutrophilic inflammation who may even deteriorate with the increase in ICS dose.

In a general population of asthmatics, our data report that 20% are obese. Ford et al [21] found that 27.3% out of 13,953 asthmatics had a BMI > 30. Female was the predominant gender in our study. As previous studies, we found the same proportion of atopic patients and similar FEV_1 and FEV_1/FVC in obese versus normal weight asthmatics [22,23]. Obese asthmatics had poorer asthma control and quality of life than those with normal weight. Only a low proportion of obese asthmatics reach asthma control with classic asthma therapy in our study which is in line with previous reports [10,11]. Our obese asthmatic population received higher doses of ICS, SABA and more frequently anti-leukotrienes and LABA than their non-obese counterpart. FVC was decreased in obese as compared to lean patients. This finding was already found by Holguin et al [23]. Alteration of thoracic mechanics may indeed contribute to greater symptom burden and poorer asthma control. As a consequence, respiratory physicians are tented to increase the dose of ICS according to GINA guidelines. However, thoracic and pulmonary compliance in those patients may be reduced due to thoracic compression by abdominal obesity. Obesity indeed reduces the downward movement of the diaphragm and change chest wall properties. These changes in the balance of forces that normally act on the lung increase the stiffness of the respiratory system [24] and reduce operating lung volumes, contributing to dyspnea [25]. A step-up in ICS dose in the absence of type 2 inflammation won't improve [26–28] and may even worsen asthma control due to side-effects.

In obese asthmatics, poor diet quality, physical inactivity and consequent excess of adipose tissue independently activates inflammatory pathways [29]. We found higher levels of blood leucocytes, CRP and fibrinogen and increased numbers of sputum neutrophils in our obese

Table 4
Proportion of good and poor responders to an ICS step-up therapy in uncontrolled asthma classified according to BMI.

	ACQ ≥ 1,5, BMI < 30	ACQ ≥ 1,5, BMI ≥ 30	P value
ICS step-up received (Y,%)	146 (26%)	57 (32%)	> 0,05
Good responders	88 (60%)	29 (53%)	> 0,05
Poor responders	33 (23%)	17 (31%)	> 0,05

ACQ: asthma control questionnaire. BMI: body mass index. ICS: inhaled corticosteroids.

asthmatic population. It was previously found that obesity is associated with systemic inflammation such as blood neutrophilia, elevated CRP and leptin levels [30]. Obesity is regarded as a low-grade chronic pro-inflammatory state that affects the cellular and molecular signaling pathways of the immune system. The total leukocyte count correlates with the degree of obesity and CRP and fibrinogen have been found to be elevated in obese asthmatics in a previous report [31]. We found higher sputum neutrophil counts in the obese subpopulation. It has been suggested that late-onset obese women have an increase in sputum neutrophils [32] and that fatty acids should activate the immune system by activation of toll-like receptors on epithelial cells conducing in nuclear translocation of NFκβ and to the production of pro-inflammatory cytokines (TNFα, IL-6 and IL-1) inducing neutrophilic inflammation [33]. We also know that exhaled air 8-isoprostane level, reflecting oxidative stress, is increased in obese asthmatics [8,34]. Scott et al. [33] have also shown that sputum neutrophils were associated with total plasma saturated fatty acids and negatively with mono-unsaturated fatty acids in men. Periyalil et al also found higher percentages of sputum neutrophils in obese versus lean asthmatics [35]. Other studies did however not find any significant increase in sputum neutrophils [36,37]. Baseline FENO values were similar to previously reported [22,23,38]. As other studies [39], we found that FENO was not correlated to BMI. In a previous study, we did not find any association between BMI and inflammatory phenotypes [40].

We looked at the predictors of a good or a poor response to ICS step-up therapy in obese uncontrolled asthmatics. Obese asthmatics who did not exhibit signs of eosinophilic inflammation but increased sputum neutrophils and low FVC were not improved by increasing the dose of ICS. The role of mechanical effects on the lungs in this subpopulation is more important and this may increase symptoms directly. This highlights the need to accurately define the contribution of obesity, as comorbidity, to the expression of asthma symptoms in patients on an individual basis. Cluster analyses and clinical observation have shown that obese asthmatics are not a uniform group. Several cluster analyses have identified two major groups of obese asthmatics that are categorized by age of onset of asthma [16] as well as TH_2 inflammation [14].

Our results suggest that phenotyping obese asthma in different inflammatory phenotypes seems as important as in non-obese asthmatics to predict the response to therapy. Previous studies have shown that weight loss resulted in a dramatic improvement in asthma control by improving lung mechanics [41] and systemic inflammation [38] but did not show any effect on bronchial inflammation on biopsy [38] or airway cellular inflammation [42]. Macgregor et al showed that weight loss in obese asthmatics was associated with a 48%–100% remission of asthma symptoms and use of asthma medication [43,44]. Dixon et al found two groups of obese asthmatics, one with early onset disease and high IgE that did not improve with surgery, and a second group with low IgE that improved with surgery [14]. Furthermore, it has been previously shown that inhaled corticosteroids treatment causes similar improvements in FEV_1 in obese than non-obese asthmatics, despite having considerably less effect on symptoms in the obese [10]. Nowadays, the current general GINA guidelines are used in obese patients but we should be aware that asthma control questionnaires may not reflect the reality of asthma control but may be influenced by obesity-related symptoms. Weight loss does not improve airway eosinophilic inflammation. It is therefore probable that weight loss induced improvements in asthma control defined as symptoms, lung function and use of medication due to a reduction in mass load on the respiratory symptoms rather than improvements in asthma per se. In adults it appears that weight loss of at least 10% is required to produce a significant improvement in asthma control [45]. De-conditioning from lack of exercise could also play a role in the relationship between obesity and the clinical expression of asthma [46]. It has been previously shown that exercise can reduce allergic airway inflammation through effects on regulatory T-cell function in a murine asthma model [47]. The approach of obese asthmatics should combine pharmacologic and non-pharmacologic therapies, including exercise, weight loss and dietary interventions and the stepping up ICS therapy should be reserved to eosinophilic phenotype. Moreover future studies must investigate how diet changes and microbiome can affect outcomes in obese asthmatics [48].

Weight reduction is likely to be at least as important as pharmacological therapy in obese adults with asthma symptoms. Whether macrolides, targeting neutrophilic inflammation could be a therapeutic option in obese asthmatics has not yet been investigated.

It has been argued that late onset non allergic obese asthma (LONA) and early onset allergic obese asthma (EOA) were characterized by different pathophysiology and response to treatment. EOA is more a type-2 disease while LONA is driven by a non type-2 inflammation. We did not find age of onset as a predictor of response to ICS treatment.

Most of the published studies on obese asthmatics have however relied on self-reporting of physician diagnosis of asthma and recall questionnaires for respiratory symptoms and medications which lead to a clear risk of misdiagnosis. In this study, asthmatics were diagnosed based on proof of airway variability or airway responsiveness to methacholine challenge. We did not exclude current smokers in our real-life study. Smoking may induce non type-2 inflammation and worsen asthma symptoms. Cigarette exposure is responsible for neutrophilic inflammation and neutrophils apoptosis leading to damage-associated molecular pattern (DAMPs), which may amplify smoking induced airway inflammation by promoting epithelial pro-inflammatory response [49]. The proportion of smokers was however similar in obese and normal-weight patients so we can suspect that smoking itself does not explain the difference seen between obese and normal weight patients in terms of asthma control. Moreover a sub analysis after exclusion of current smokers confirmed the same predictors of response to inhaled corticosteroids. Smoking cessation however remain of upmost importance in the management of asthmatics.

Our results suggest that respiratory physicians should measure inflammation, especially in these obese patients, to avoid unnecessary step-up in ICS dose related to persistent symptoms of dyspnea. In the presence of a “type-2” pattern, ICS will improve asthma symptoms while in the presence of neutrophilic inflammation or a restriction profile, weight loss may improve asthma outcomes and treatment should involve bronchodilators and low to moderate doses of ICS. Obesity is a well-known comorbidity in asthma and should be targeted in addition to the treatment of cortico-sensitive inflammation. Future research should aim to find novel biomarkers that might help identify these sub-phenotypes [50].

In our unselected population of asthmatic, we found that markers of bronchial eosinophilic inflammation such as FeNO [51,52] and sputum eosinophils predict a good response to ICS in obese asthmatics while a restrictive pattern and neutrophilic inflammation may identify a subgroup of patients that can deteriorate with the increase in ICS dose. In those patients, management of obesity should be the first choice. Increasing corticosteroid doses based on poor asthma control, as currently recommended in current guidelines, may thus lead to ICS overtreatment in non-eosinophilic obese asthma. Much attention should be paid to eosinophilic markers in this particular population of asthmatics.

CRediT authorship contribution statement

S. Peerboom: Conceptualization, Methodology, Data curation. **S. Graff:** Methodology, Data curation. **L. Seidel:** Formal analysis, Data curation. **V. Paulus:** Data curation. **M. Henket:** Data curation. **C. Sanchez:** Data curation. **F. Guissard:** Data curation. **C. Moermans:** Data curation. **R. Louis:** Conceptualization, Writing - review & editing. **F. Schleich:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Writing - original draft, Writing - review & editing.

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