Respiratory Medicine 135 (2018) 22–28

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

Mucus hypersecretion in asthma is associated with rhinosinusitis, polyps and exacerbations☆

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ARTICLE INFO

Keywords:
Asthma
Mucus hypersecretion
Nasal polyps
Rhinosinusitis
Anosmia
Asthma phenotype

ABSTRACT

Background: Bronchial hypersecretion is a poorly studied symptom in asthma. The aim of the study was to determine the specific characteristics of asthmatics with bronchial hypersecretion.
Methods: A total of 142 asthmatics (21.8% men; mean age 49.8 years) were prospectively followed for one year. Mucus hypersecretion was clinically classified into two severity categories: daily sputum production and frequent expectoration but not every day. Clinical and pulmonary function variables associated with mucus hypersecretion were assessed by multiple logistic regression analysis.
Results: Daily cough was recorded in 28.9% of patients and sputum production daily or most of the days in 52.1%. Patients with mucus hypersecretion had more dyspnoea, poorer asthma control and quality of life, had suffered from more exacerbations and showed anosmia associated with chronic rhinosinusitis and nasal polyposis more frequently. Factors associated to mucus hypersecretion were anosmia, one exacerbation or more in the previous year and FEV1/FVC < 70% (AUC 0.75, 95% CI 0.66–0.85) for the first definition of hypersecretion, and anosmia, poor asthma control and age (AUC 0.75, 95% CI 0.67–0.83) for the second definition.
Conclusions: Mucus hypersecretion is frequent in patients with asthma, and is associated with chronic upper airways disease, airway obstruction, poor asthma control and more exacerbations.

1. Introduction

The viscoelastic properties of airway mucus play a central role for optimal efficiency of ciliary interaction and effective defense mechanisms, including entrapment and removal of inhaled particles (and bacteria) and humidification of the airways [1–3]. Excessive mucus production or impaired clearance are involved the pathogenesis of common airways diseases [4]. However, our understanding of molecular mechanisms of mucin overproduction and secretion in inflammatory lung disease remains limited.

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https://doi.org/10.1016/j.rmed.2017.12.013
Received 1 November 2017; Received in revised form 23 December 2017; Accepted 30 December 2017
Available online 03 January 2018
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Abbreviations list

COPD	Chronic Obstructive Pulmonary Disease
FEV_1	Forced Expiratory Volume in one second
BAL	Bronchoalveolar lavage
BMI	Body Mass Index
ARIA	Allergic Rhinitis and Its Impact on Asthma
GEMA	Spanish Guidelines for the Management of Asthma
mMRC	modified Medical Research Council
ACT	Asthma Control Test
AQLQ-S	Sidney Asthma Quality of Life Questionnaire
SEPAR	Spanish Society of Pneumology and Thoracic Surgery
FVC	Forced Vital Capacity
FeNO	Fractional exhaled Nitric Oxide
ATS	American Thoracic Society
ERS	European Respiratory Society
SD	Standard Deviation
OR	Odds Ratio
CI	Confidence Interval
AUC	Area Under the curve
ROC	Receiver Operating Characteristics

Airways mucus hypersecretion is a feature of many patients with chronic obstructive pulmonary disease (COPD) and asthma contributing to morbidity and mortality. Chronic mucus hypersecretion has been associated with excess decline of forced expiratory volume in one second (FEV_1) and increased risk of hospitalizations because of COPD [5]. Mucus hypersecretion has been also identified as a risk factor for death from COPD [6]. In bronchial asthma, chronic mucus hypersecretion was found a significant marker of accelerated decline in FEV_1 [7] and severity of disease [8]. Also, a relationship between mucus hypersecretion and *Chlamydophila pneumonia* has been reported [9] as well as high proportion of eosinophils in bronchoalveolar lavage (BAL) samples [10] and blood eosinophilia in asthma patients with excess mucus [11]. Excess mucus not only obstructs airways but also contributes to airways hyperresponsiveness [1]. Mucus in patients with asthma has particular features, including predominant expression of mucin MUC5AC associated with higher plasma exudation, in contrast to MUC5B strongly expressed in patients with COPD [1]. Mucus plugs of asthmatic patients, unlike those in COPD, are easily adhered to the epithelium and difficult to dislodge from the airways, a fact that has been related to a lower release of proteases to cleave mucins attached to the surface of globet cells as compared to other types of respiratory diseases (COPD, bronchiectasis) [1].

Clinical data of hypersecretion in asthma are heterogeneous. Mucus hypersecretion has not been the primary variable in some studies [7,12], while in others, the statistical power is limited by the small study population [10]. Also, different criteria have been used to assess mucus hypersecretion or to grade the quantity of sputum, ranging from the typical question '*Have you cough for at least 3 months in at least 2 consecutive years?*' used for the definition of chronic bronchitis [7,13,14] or to the presence of cough or of an increase in sputum [12]. On the other hand, coughing is not always accompanied by expectoration and variable quantities and patterns of sputum production may be present in asthma patients with hypersecretion.

The objective of this study was to compare the characteristics of asthmatic patients with and without mucus hypersecretion. We hypothesized that the intensity of expectoration (persistent or intermittent) would be associated with differential features in the clinical profile and lung function of hypersecretory asthmatic patients.

2. Material and methods

2.1. Study design and participants

This was a prospective, observational and multicentre study of one year duration. The study was carried out in the outpatient asthma clinics of nine hospitals throughout Spain belonging to the public National Health Care System. The study was conducted according to the principles of the Declaration of Helsinki (18th World Medical Assembly) and was approved by the Clinical Research Ethic Committee of Hospital Germans Trias i Pujol in Badalona, Barcelona (Spain). The committee's reference number was EO-11-117. Written informed consent was obtained from all participants.

Patients with clinically stable asthma defined as absence of exacerbations in the previous month were eligible provided that the following inclusion criteria were fulfilled: age older than 18 years, a clinical diagnosis of asthma with a positive bronchodilation test with $FEV_1 > 12\%$ and 200 mL after 200 μg inhaled salbutamol or a positive inhaled methacholine challenge test [15,16], and absence of respiratory infection during previous month. Current smokers or ex-smokers were excluded from the study as were patients with a previously diagnosed respiratory disease, such as bronchiectasis or COPD.

2.2. Procedures and data collection

Patient assessments were performed on inclusion in the study. Demographic data (age, sex), body mass index (BMI), age at onset of asthma, duration of disease, treatment with oral steroids within previous 12 months, history of emergency room and hospital admissions throughout life and within the previous 12 months, and number of exacerbations requiring antibiotic, in addition to oral steroids, within the previous 12 months were recorded. The presence of rhinitis, sinusitis and nasal polyposis was evaluated according to the classification of severity of rhinitis of The Allergic Rhinitis and Its Impact on Asthma (ARIA) document [17] and EPOS guidelines on rhinosinusitis and nasal polyps [18]. Severity of asthma was classified according to the Spanish Guidelines for the Management of Asthma (GEMA) [19]. Atopy was evaluated using a skin prick test for a panel of common aeroallergens, with positive results when the wheal diameter was > 3 mm [20]. The modified Medical Research Council (mMRC) scale was used in the assessment of dyspnoea [21]. The degree of asthma control was evaluated according to the Asthma Control Test (ACT) [22] (an ACT score ≤ 15 identified poorly-controlled asthma patients). Also, patients completed a Spanish validated version of the Sidney Asthma Quality of Life Questionnaire (AQLQ-S), which comprises 20 items with a 4-week recall period [23,24]. Items are grouped into four domains (breathlessness: five items, mood: five items, social: seven items, concerns: three items). Items are assessed using a 5-point Likert scale. The score of each domain is calculated by the sum of each item divided by the number of items and multiplied by 2.5. The total score ranges from 0 to 10, with lower ratings indicate less impairment (better quality of life).

A spirometry with bronchodilator test was performed according to recommendations of the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) [15]. Spirometric parameters (FEV_1, forced vital capacity [FVC]) were recorded at the time of visit or during the previous 3 months. Airway inflammation was measured by fractional exhaled nitric oxide (FeNO) following recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [25]. Blood eosinophil count and total serum IgE levels were also measured.

Mucus hypersecretion was evaluated according to four possible mutually exclusive responses to the question '*How often do you expectorate*?', which included *1*: every day; *2*: some days, but others not; *3*: only in association with colds; *4*: no sputum production. Two definitions of mucus hypersecretion were established. The first included all patients that marked *1* (daily sputum production) and the second all

patients that marked *1* or *2* (daily sputum expectoration, and frequent sputum production but not every day, independently of asthma exacerbations).

Patients were visited after 12 months of inclusion in the study. ata recorded included exacerbations requiring antibiotic treatment, oral steroids, or both, and emergency room and hospital admissions due acute asthma episodes. Spirometry was also repeated.

2.3. Statistical analysis

Quantitative variables are expressed as mean and standard deviation (SD) and categorical variables as frequencies and percentages. Quantitative variables were compared with the Student's *t*-test or the Mann-Whitney *U* test according to the normal or non-normal distribution of data. Categorical variables were compared with the chi-square (χ^2) test. Multiple logistic regression analysis was used to assess independent variables associated with the first and second definition of mucus hypersecretion. The variables that were statistically significant in the univariate logistic regression analysis were included. The odds ratio (OR), 95% confidence interval (CI) and the area under the receiver operating characteristics (ROC) curve (AUC) were calculated. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 21.0 for Windows. Statistical significance was set at $P \leq .05$.

3. Results

3.1. Characteristics of patients

A total of 142 patients were included in the study. There were 31 men and 111 women with a mean (SD) age of 49.8 (17) years. Asthma was persistently severe in 54.2% of patients, poorly-controlled asthma (ACT score ≤ 15) in 22.7% and FEV_1/FCV ratio < 70% in 48%. The prevalence of rhinitis, sinusitis and nasal polyposis was 70.4%, 24.8% and 12%, respectively. Other characteristics are summarized in Table 1. Mucus hypersecretion according to the first definition was recorded in 41 patients (28.9%) and according to the second definition in 74 (52.1%).

3.2. Comparison of patients with and without mucus hypersecretion

The distribution of variables in patients with and without mucus hypersecretion according to the two definitions of hypersecretion is shown in Table 2. Patients with hypersecretion were significantly older, with a longer duration of disease and had severe asthma more frequently; numerically and statistically significant for the first definition and numerically for the second Other significant variables included a higher degree of dyspnea (mMRC score), poorer quality of life in the domains of mood, social, concern and total score of the AQLQ-S, greater airflow obstruction (FEV_1/FVC ratio, percentage of patients with FEV_1/FVC < 70%) and higher number of emergency room visits during the patient's life and in the previous 12 months. Also, during the follow-up period of 12 months, patients with mucus hypersecretion had more exacerbations than patients without mucus hypersecretion, with statistically significant differences for both definitions of hypersecretion (Fig. 1). The percentage of patients with severe rhinitis, sinusitis, nasal polyps and anosmia was also significantly higher among patients with mucus hypersecretion for both definitions (Table 2).

3.3. Factors associated with mucus hypersecretion

In the multiple logistic regression analysis, independent variables significantly associated with mucus hypersecretion according to the first definition were anosmia, number of exacerbations in the previous 12 months and FEV1/FVC < 70% (Table 3). For this model, the AUC was 0.75, 95% CI 0.66–0.85, $P = .000$ (Fig. 2). When the second definition of mucus hypersecretion was used, variables significantly associated with hypersecretion were anosmia, age (for each year of increase in age, there was a 3% increase in the risk of being a hypersecretory asthmatic patient) and ACT score (for each one point decrease in the ACT, the risk of being a hypersecretory asthmatic patient increased by 13%) (Table 3). The AUC of this model was 0.75, 95% CI 0.67–0.83, $P = .000$ (Fig. 2).

4. Discussion

Mucus hypersecretion was a prevalent symptom in the present study. Between one third and half of the patients depending on the definition of hypersecretion, reported sputum production within symptom constellation. Hypersecretory asthmatic patients as compared to non-hypersecretory counterparts were older, suffered from more symptoms and showed greater impairment of quality of life, airways obstruction and more exacerbations. Interestingly, mucus hypersecretion was associated with upper respiratory tract disease, including anosmia, nasal polyposis and sinusitis.

The present findings are consistent with other studies. In a study of Openshaw and Turner-Warwick [13] of 130 patients with asthma, 43% had sufficiently prolonged or recurrent sputum production (irrespective of changes in volume during asthma attacks) to fulfil the criteria for chronic bronchitis in accordance with the MRC definition [14]. Other studies have evaluated mucus hypersecretion together with other variables as a predictive factor of asthma severity, degree of airway obstruction or to classify different asthma phenotypes. It should be noted that in contrast to our study population, smokers or ex-smokers were included in these studies. Lange et al. [7] in a 15-year follow-up study using data of the Copenhagen City Heart Study, chronic mucus hypersecretion was found in 63% of men and in 54% of women with asthma. In both sexes, the presence of mucus hypersecretion and smoking was associated with a greater decline in FEV_1. Connolly et al. [12] in a cross-sectional study designed to assess the relevance of sputum production to pulmonary function found a prevalence of chronic sputum in a high percentage of non-smoking men (29%) and

Table 1
General characteristics of 142 patients with stable asthma included in the study.

Variable	Frequency
Sex, men/women	31/111
Age, years, mean (SD)	49.8 (17.0)
Body mass index, kg/m^2, mean (SD)	26.9 (4.0)
Age at onset of asthma, years, mean (SD)	30 (18)
Duration of disease, years, mean (SD)	29.7 (18.0)
Atopy, positive skin prick test (n = 138), no. (%)	85 (61.6)
Symptoms and treatment, mean (SD)	
Asthma control, ACT score	19.1 (5–0)
Dyspnoea, mMRC score	0.87 (0.9)
Inhaled steroids, budesonide, μg/day	834 (705)
Oral steroids, mg/year	415 (932)
Injectable steroids, number of courses[a]	0.24 (0.9)
Pulmonary function, mean (SD)	
FEV_1, %	80.6 (21.0)
FVC, %	91.9 (18.0)
FEV_1/FVC, %	69.5 (12.0)
Use of resources, mean (SD)	
Hospital admission	
Lifelong history	2 (6.5)
Previous 12 months	0.08 (0.4)
Emergency department visits	
Lifelong history	13.3 (30.0)
Previous 12 months	0.5 (1.0)
Intensive care unit admission	0.13 (0.4)
Exacerbations in previous 12 months	1.4 (1.9)

SD: standard deviation; ACT: Asthma Control Test; mMRC: modified Medical Research Council.
[a] Intramuscular triamcinolone.

Table 2
Differences between patients with and without mucus hypersecretion with respect to definition.

Variables	Mucus hypersecretion, first definition[a]			Mucus hypersecretion, second definition[b]		
	Present	Absent	OR (95% CI), *P* value	Present	Absent	OR (95% CI), *P* value
Total patients	41	101		74	68	
Women, %	80.5	77.2	1.21 (0.49–2.99)	75.7	80.9	0.73 (0.32–1.64)
Age, years, mean (SD)	55.4 (14.0)	47.5 (18.0)	1.03 (1.01–1.05) *P* < .05	54.4 (16.0)	44.7 (20.0)	1.04 (1.01–1.06) *P* < .05
BMI, kg/m^2, mean (SD)	27.4 (4.7)	26.7 (4.5)	1.04 (0.96–1.21)	27.4 (4.8)	26.3 (1.2)	1.06 (0.98–1.13)
Age at onset, years, mean (SD)	30.2 (20.0)	29.5 (17.5)	1.0 (0.98–1.0)	32.4 (18.4)	26.8 (17.7)	1.02 (0.99–1.04)
Duration of disease, years, mean (SD)	24.8 (14.0)	18.0 (14.0)	1.03 (1.01–1.06) *P* < .05	21.7 (13.0)	18.1 (15.0)	1.02 (0.99–1.04)
Patients with severe asthma, %	70.7	47.5	2.67 (1.23–5.81) *P* < .05	59.5	48.5	1.56 (0.80–3.02)
ACT score, mean (SD)	18.6 (5.0)	18.9 (5.0)	1.03 (0.96–1.10)	17.9 (5.0)	20.4 (4.0)	1.11 (1.03–1.19) *P* < .05
Dyspnoea, mMRC score, mean (SD)	1.1 (0.9)	0.8 (0.9)	1.44 (0.97–2.13) *P* < .05	1.04 (0.8)	0.69 (0.9)	1.56 (1.05–2.32) *P* < .05
AQLQ-S score, mean (SD)						
Breathless	2.73 (2.5)	2.45 (2.6)	1.01 (0.97–1.20)	3.1 (2.7)	1.9 (2.3)	1.21 (1.05–1.40)
Mood	3.9 (3.0)	2.9 (3.3)	1.09 (0.97–1.22)	3.9 (3.4)	2.5 (2.8)	1.15 (1.03–1.29) *P* < .05
Social	3.1 (3.0)	2.3 (2.7)	1.09 (0.96–1.24)	3.1 (3.0)	1.9 (2.4)	1.17 (1.03–1.33) *P* < .05
Concern	3.5 (3.0)	2.4 (2.7)	1.15 (1.01–1.30) *P* < .05	3.3 (2.9)	2.1 (2.6)	1.17(1.03–1.33) *P* < .05
Total score	3.3 (2.7)	2.5 (2.6)	1.11 (0.96–1.27)	3.3 (2.7)	2.2 (2.4)	1.19 (1.03–1.37) *P* < .05
Inhaled steroids, mg/day, mean (SD)	937 (596)	795 (743)	1.0	902 (656)	764 (751)	1.0
Oral steroids, mg/day, mean (SD)	365 (562)	435 (1048)	1.0	425 (689)	403 (1145)	1.0
Triamcinolone i.m., mean (SD)	0.29 (1.0)	0.22 (1.0)	1.08 (0.75–1.55)	0.23 (0.8)	0.25 (1.0)	1.02 (0.72–1.45)
Positive skin pick test, % pts.	64.1	60.6	1.61 (0.54–2.50)	61.1	62.1	0.96 (0.48–1.90)
Blood eosinophils, mean (SD)						
Absolute count, μL	365 (293)	402 (930)	1.0	321 (270)	473 (1134)	1.0
Percentage	5 (4)	4.3 (3.0)	1.05 (0.94–1.17)	4.4 (3.7)	4.7 (3.4)	1.02 (0.92–1.13)
Total serum IgE, mg/dL, mean (SD)	127 (151)	289 (591)	1.0	194 (359)	291 (625)	1.0
FEV_1%, mean (SD)	74 (20)	83 (21)	1.02 (1.00–1.04) *P* < .05	77.5 (21)	83.9 (21)	1.01 (0.99–1.03)
FVC %, mean (SD)	87.4 (19)	93.8 (17)	1.02 (0.99–1.04)	89.8 (19)	94.3 (16)	1.01 (0.99–1.03)
FEV_1/FVC ratio, mean (SD)	64.6 (11)	71.5 (12)	1.05 (1.01–1.08) *P* < .05	67 (12)	72.1 (12)	1.04 (1.01–1.07) *P* < .05
FEV_1/FVC < 70%, % pts.	64.1	41.7	2.50 (1.16–5.4) *P* < .05	58.6	36.9	2.41 (1.21–4.83) *P* < .05
FeNO, ppb, mean (SD)	30.1 (24)	34 (31)	0.99 (0.98–1.02)	33.9 (34)	32.2 (25)	1.01 (0.99–1.02)
Hospital admission (≥1), % pts.						
Lifelong	46.3	46.5	0.99 (0.48–2.05)	43.2	50	0.76 (0.39–1.48)
Previous 12 months	9.8	5	2.08 (0.53–8.16)	12.2	0	
Emergency room visits, % pts.						
Lifelong (> 3)	65.9	48.5	2.05 (0.96–435)*P* < .05	62.2	44.1	2.08 (1.06–4.07) *P* < .05
Previous 12 months (≥1)	39.0	24.8	1.65 (0.76–3.61)	41.9	14.7	1.98 (0.99–2.95) *P* < .05
ICU admission (≥1), % pts.	12.2	8.9	1.098 (0.36–3.31)	9.5	10.3	0.704 (0.221–2.295)
Exacerbations 12 months, mean (SD)	2.15 (2.7)	1.10 (1.4)	1.30 (1.07–1.59) *P* < .05	1.88 (2.2)	0.9 (1.4)	1.40 (1.10–1.78) *P* < .05
Rhinitis, % pts.	73.2	69.3	1.09 (0.49–2.39)	67.6	73.5	0.86 (0.42–1.74)
Severe rhinitis, % pts.	53.1	29.0	2.35 (0.89–6.18) *P* < .05	44.4	28.0	1.91 (0.88–4.16)
Sinusitis, % pts.	48.8	20	3.63 (1.67–7.90) *P* < .05	35.6	20.6	2.22 (1.04–4.71) *P* < .05
Nasal polyposis, % pts.	34.2	15.8	2.75 (1.19–6.37) *P* < .05	27.1	14.7	2.15 (0.92–5.0) *P* < .05
Anosmia, % pts.	29.3	5.0	7.94 (2.59–24.4) *P* < .05	18.9	4.4	5.06 (1.39–18.46) *P* < .05

SD: standard deviation; ACT: Asthma Control Test; mMRC: modified Medical Research Council; AQLQ-S: Sidney Asthma Quality of Life questionnaire; pts: patients; FeNO: fractional exhaled nitric oxide; ICU: intensive care unit.

[a] Answer '1' (every day).

[b] Answer '1' (every day) or '2' (some days, but others not) to the question *How often do you expectorate?*.

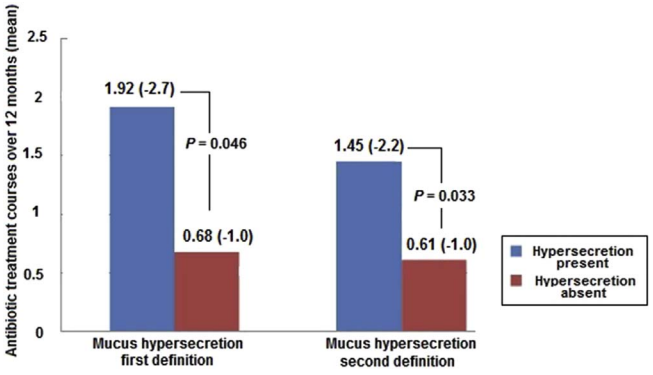


Fig. 1. Mean number of exacerbations over 12 months of follow-up in patients with mucus hypersecretion according to the first definition (expectoration present every day) and second definition (expectoration present every day and some days, but others not).

women (34%). In an analysis of cross-sectional data from 61 smokers and 59 never smokers with asthma, chronic mucus hypersecretion occurred in 56% and 20% of smokers and never smokers, respectively

Table 3
Results of multiple logistic regression analysis depending on the definition of mucus hypersecretion.

Variables	Odds ratio (95% confidence interval)	*P* value
Mucus hypersecretion, first definition[a]		
Anosmia	7.7 (2.1–28.7)	.002
Airflow obstruction (FEV_1/FVC < 70%)	2.6 (1.1–6.4)	.030
Exacerbations in the previous 12 months	1.25 (1.01–1.4)	.041
Mucus hypersecretion, second definition[b]		
Anosmia	5.3 (1.03–27)	.046
ACT score	1.13 (1.03–1.23)	.013
Age	1.03 (1.01–1.06)	.011

ACT: Asthma Control Test.

[a] Answer '1' (every day) and.

[b] Answer '1' (every day) or '2' (some days, but others not) to the question *How often do you expectorate?*.

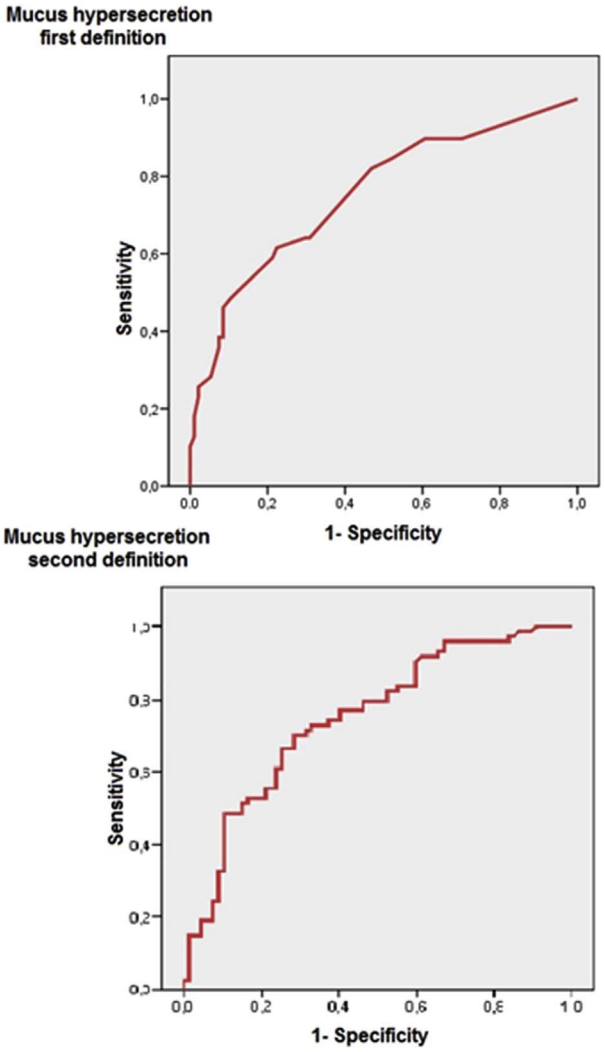


Fig. 2. ROC curves for regression models with the first definition of mucus hypersecretion (expectoration present every day) (AUC 0.75, 95% CI 0.66–0.85) and the second definition (expectoration present every day and some days, but others not) (AUC 0.75, 95% CI 0.67–0.83).

[26]. The prevalence of chronic hypersecretion in the different studies varies depending on smoking status and criteria used for defining sputum production, such as the definition of chronic bronchitis (occurrence of chronic sputum for at least 3 months in at least 2 consecutive years) or other responses to questions used to grade the pattern and/or quantity of sputum production [13]. We used a single question with four possible responses to assess the frequency of sputum production, according to which two definitions of hypersecretion were established. Using a restrictive criterion of bringing up phlegm every day, the prevalence of hypersecretion was 28.9%, but increased to 52.1% when using a broader definition that included patients reporting sputum production some days but others not.

Mucus hypersecretion has shown a detrimental effect on lung function, particularly in association with active smoking [7,12], although similar findings were observed in our study in which current smokers and ex-smokers were excluded. Mechanisms underlying the relationship of mucus hypersecretion with airway obstruction are partially known, with airway thickening and mucus plugging occluding the airways [27–29]. In mice, overexpression of mucin MUC5AC has been related to airway wall thickening. FOXA2 is transcriptional repressor of mucin biosynthesis. The MUC5AC gene product is upregulated in the airways of asthmatic patients. Studies in FOXA2 knockout mice showed that the absence of this regulator causes an increase in MUC5AC gene expression and cytokine IL-13 expression that is known to be associated with airway inflammation [30]. Helper T-cell type 2 cytokines, including IL-13, are implicated in mucus production and globet cell hyperplasia in asthma [31]. Dysregulation of FOXA2, MUCA5AC and IL-13 signal pathways may contribute, at least in part to bronchial wall thickening and excessive mucus production is asthmatic patients. Infection may play also a role in promoting mucin overproduction. Morinaga et al. [8] showed that *C. pneumonia* induced MUC5AC production in bronchial epithelial cells. Also, cells pretreated with macrolides and ketolides reduced *C. pneumonia*-induced MUC5AC production. In mouse lungs, Hao et al. [32] demonstrated that *Mycoplasma pneumonia* infection induced the expression of mucins MUC5AC and MUC5B by activating the STAT6-STAT3 and epidermal growth factor receptor (EGFR) signal pathways, which in turn downregulated FOXA2.

As expected, pathophysiological changes observed in airways of patients with asthma had clinical repercussions as shown by a more severe asthma in the presence of mucus hypersecretion [10,26]. In our study, patients with mucus hypersecretion showed a higher number of exacerbations in the previous 12 months as well as over the 12-month follow-up observational period, with significant differences as compared to patients without hypersecretion. This finding was also independent of whether the first or the second definition of mucus hypersecretion was used.

A clinically interesting observation was the high percentages of patients in the group of mucus hypersecretion with sinusitis, nasal polyposis and severe rhinitis. A relationship between mucus hypersecretion and upper airways respiratory disease in asthma has not been previously reported. Smyrnios et al. [33] in 71 patients who complained of expectoration greater than 30 Ml of sputum per day, found that postnasal drip syndrome was the single most common cause of excessive sputum production (40% of cases). It seems plausible that the pathophysiological mechanisms involved in mucus hypersecretion in the lower airways may also be responsible for the development of upper airways disease. Luo et al. [34] showed downregulation of FOXA2 and upregulation of both MUC5AC and MUC5B in patients with chronic rhinosinusitis. In this study, the use of clarithromycin decreased MUC5AC expression *in vitro* [34]. These observations contribute to explain the striking association of mucus hypersecretion and the presence of rhinosinusitis and nasal polyposis found in our patients. Therefore, upper airways disease should be investigated in patients with asthma, particularly in those with excessive mucus.

The present findings should be interpreted taking into account some limitations. An *ad hoc* definition of mucus hypersecretion was used. The idea was to identify on clinical grounds as strictly as possible a group of patients with hypersecretion. To this purpose, in the first definition, only patients with daily sputum production were accepted. However, using this definition, the profile of some patients with hypersecretion could have been inadvertently excluded and, for this reason, the second definition covered patients who also reported frequent sputum production but not daily and independently of exacerbations. However, validated methods for reliable quantification of sputum production are lacking, and assessment of chronic mucus hypersecretion by measurements of sputum volume or standardized questions on phlegm production seems to provide similar results [35]. Also, a deleterious effect of mucus hypersecretion on decline of lung function could not be demonstrated, probably because of the reduced number of patients and the short follow-up period. The high percentage of patients with severe asthma is explained because study participants were recruited in the hospital setting. This selection bias limits the external validity of the study. The presence of an aspirin exacerbated respiratory disease was not assessed. Also, there was an imbalance between male (n = 31) and female (n = 111) patients. The gender disparity that exists in asthma prevalence is probably the reason for a higher number of women as compared to men included in the study [36]. In fact, severe asthma was documented in 54.2% of our patients, and is well-known that women are more likely to have severe asthma compared to men (women have a

three-fold possibilities of being hospitalized for asthma exacerbation than men). Also, it has been shown that estrogen increases and testosterone decreases Th2-mediated airway inflammation, and that females have increased IL-17A-mediated airway inflammation compared to males [37].

5. Conclusions

In summary, mucus hypersecretion is frequently observed in patients with asthma especially in those with severe disease, and was associated with chronic upper airways disease, poor asthma control and more exacerbations. Investigation of anosmia, rhinosinusitis and nasal polyposis in the presence of mucin hypersecretion in asthmatic patients is clinically relevant.

Author's contributions

CMR carried out the study design, recruitment of patients, statistical analysis, interpretation of analysis, writing of the manuscript. AC carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. CPS carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. JLGR carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. APS carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. NMM carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. SPE carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. AP carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. SMA carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. VP carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. ALV carried out the recruitment and care of the patients, critical review of the manuscript and approval of the final draft. CP carried out the recruitment and care of the patients, interpretation of analysis, writing of the manuscript, approval of the final draft. All authors read and approved the final manuscript.

Conflicts of interest

C. Martinez-Rivera has received fees as a speaker from BoehringerIngelheim, Chiesi, GlaxoSmithKline, Merck and Novartis.

A. Crespo none to be declared.

C. Pinedo-Sierra none to be declared.

J.L. García-Rivero has received fees as a speaker from Almirall, BoehringerIngelheim, Pfizer, AstraZeneca, Chiesi, GlaxoSmithKline, Menarini, Takeda, Teva, Ferrer and Novartis, and consulting fees from Almirall, BoehringerIngelheim and Menarini.

A. Pallarés-Sanmartín has received honoraria for conferences in educational events from GlaxoSmithKline, Boehringer Ingelheim, Mundipharma, AstraZeneca, Novartis, Teva, Chiesi and Esteve.

N. Marina Malanda none to be declared.

S. Pascual-Esquicia none to be declared.

A. Padilla none to be declared.

S. Mayoralas-Alises none to be declared.

V. Plaza in the last three years received honoraria for speaking at sponsored meetings from Chiesi, Esteve Laboratories, GlaxoSmithKline, Novartis, Orion and Pfizer. Received help assistance to meeting travel from Chiesi and Novartis. Act as a consultant for MundiPharma, Orion and Teva. And received funding/grant support for research projects from a variety of governmental agencies and not-for-profit foundations, as well as AstraZeneca, Chiesi and Menarini.,GlaxoSmithKlein, and ALK.

A. López-Viña in the last three years has been on advisory boards and has received speaker's honoraria from, TEVA, GlaxoSmithKline, Novartis, Mundipharma, Chiesi, Boehringer Ingelheim, and Pfizer.

C. Picado none to be declared.

Fundings

None.

Acknowledgments

The authors thank Marta Pulido, MD, for editing the manuscript and editorial assistance. The fees for medical editing were paid Respira-Fundación Española del Pulmón-Separ.

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