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Inhaled corticosteroid response in smoker versus non-smoker asthmatic patients: a cross-sectional study

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Abstract

Background: Asthmatic smokers are a distinct phenotype of asthma. There is a lack of specific information about the treatment of asthma in smokers. The purpose of this study was to compare the effects of inhaled corticosteroid (ICS) on asthmatic smokers and non-smokers.

Results: The present observational, cross-sectional study was conducted at the Chest Department in Assiut University Hospital, during the period from August 2018 to January 2020. Hundred and seventeen asthmatic patients (42 smokers, 30 ex-smokers, and 45 non-smokers) were assessed using an asthma control questionnaire (ACQ), spirometry, sputum cytology, and serum periostin and eotaxin-2 to compare between a patient on inhaled corticosteroid for at least 3 months and patients who do not receive any form of corticosteroid. Asthmatic smokers had poor response to ICS and had insignificant improvement as regard all parameters. However, asthmatic ex-smokers had a partial response to ICS. They had higher post-bronchodilator FEV1 in comparison to those who did not receive ICS. Asthmatic non-smokers on ICS showed the best response as they were well controlled as regard ACQ. Moreover, they had higher post-bronchodilator FEV1/FVC, post-bronchodilator FEV1, and post-bronchodilator FEF25-75, and lower sputum eosinophils and neutrophils.

Conclusion: Smoking adversely affects the course and response to ICS therapy in asthma.

Trial registration: Interrelation between bronchial asthma and smoking: ClinicalTrials.gov ID: NCT03207620. Registered 27 June 2017.

Keywords: ICS, Asthma, Smoking, Phenotype, Periostin, Eotaxin-2, Eosinophil, Neutrophil, Smokers

Background

Asthma is now recognized as a heterogeneous entity that is complex to treat. The subdivision of asthma, provided by "cluster" analyses, has revealed various groups of asthma patients who share phenotypic features. These phenotypes underlie the need for personalized asthma therapy because, in contrast to the previous approach, treatment must be tailored to the individual patient. Determination of the patient's asthma phenotype is therefore essential but sometimes challenging [1].

Smoking is associated with a higher incidence of asthma and asthmatic smokers likely represent a distinct phenotype of the disease. However, clinical trials studying new drugs or newer therapeutic regimens for asthma generally exclude smokers. Therefore, there is a lack of specific information about the treatment of asthma in smokers [2].

Corticosteroid insensitivity is an important clinical feature of asthma, particularly in patients with severe disease and smokers. The mechanisms of corticosteroid

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insensitivity in asthmatic patients are poorly understood [3].

The present study aimed to compare the effects of inhaled corticosteroid on asthmatic smokers and non-smokers and detect the effect of inhaled corticosteroid on the level of serum periostin and eotaxin-2.

Methods

Study design

Observational, cross-sectional study registered (ClinicalTrials.gov ID: NCT03207620) study. The study was done at the Chest Department and Chest Outpatient Clinic in Assiut University Hospital, Faculty of Medicine, Assiut University, in the period from August 2018 to January 2020. The study design was approved by the Scientific Ethics Committee of the Faculty of Medicine of Assiut University. After meeting inclusion criteria, informed consent is obtained from the patient.

Patient selection

The study included 117 asthmatic patients (42 smokers, 30 ex-smokers, and 45 non-smokers) randomly selected from patients attended at Chest Out-patient Clinic in Assiut University Hospital (Fig. 1).

Features used in making the diagnosis of asthma according to GINA guidelines 2020: A history of variable respiratory symptoms: (Typical symptoms were wheeze, shortness of breath, chest tightness, and cough). People with asthma generally had more than one of these symptoms. The symptoms occurred variably over time and vary in intensity. The symptoms often occurred or were worse at night or on waking. Symptoms were often triggered by exercise, laughter, allergens, or cold air. Symptoms often occurred with or worsen with viral infections. Evidence of variable expiratory airflow limitation: At least once during the diagnostic process (e.g., when FEV1 is low), a document that the FEV1/FVC ratio was below the lower limit of normal. A document that variation in lung function was greater than in healthy people, for example, excess variability was recorded if: o FEV1 increases by > 200 mL and > 12% of the baseline value after inhaling a bronchodilator. This is called significant bronchodilator responsiveness or reversibility [4].

Inclusion criteria

Stable asthmatic patients (however, smokers, ex-smoker, or non-smokers) were included (stable asthmatic defined as no emergency clinic or hospital visit, oral corticosteroid prescription, or change in asthma treatment in the past month), and current smoking was defined as 5 or more cigarettes per day and a smoking history of 5 pack-years or greater [3], while ex-smoker was defined as they had ceased smoking for 6 months. Age (18-45) years old, male patients, treatment with long-acting b2-agonists, and leukotriene receptor antagonists were

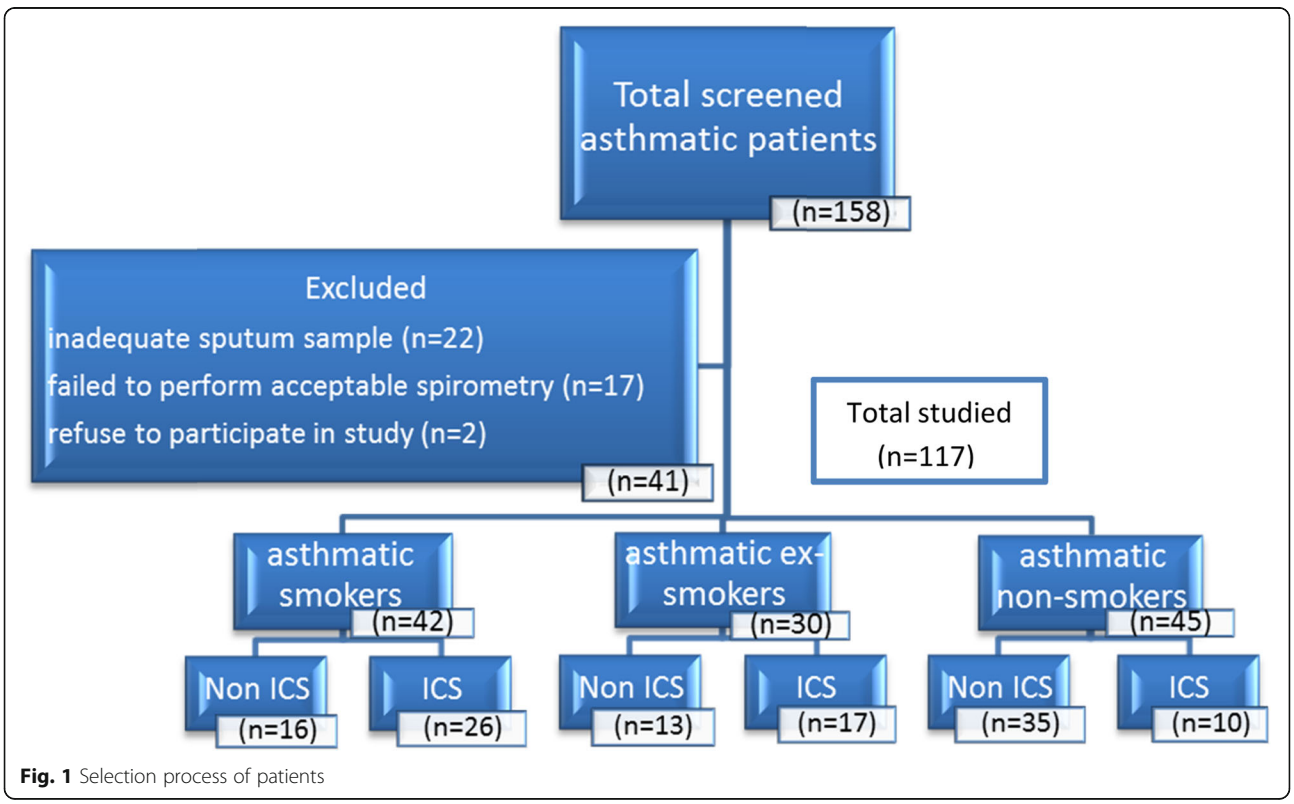

Fig. 1 Selection process of patients

allowed. Each of the studied groups was classified into two subgroups regarding inhaled corticosteroid (ICS) use: those who were on ICS for at least 3 months and those who were not on ICS.

Exclusion criteria

Acute severe asthma, any causes of airway obstruction other than asthma as COPD patients, bronchiectasis, etc., age < 18 and > 45 years old, body mass index > 35, patients required treatment with systemic corticosteroids in the last 1 month and the patients who stopped smoking in duration less than 6 months.

Eligibility for the study required demonstration of reversible airflow obstruction (FEV1 bronchodilator response to b2 agonist of > 12% [and > 200 mL]) [5]. All lung function assessments met relevant international consensus guidelines.

Sample size calculation

Sample size calculation was carried out using the G* Power 3 software [6]. Based on previously reported prevalence of asthma in Egyptian people that was 7.6% [7] with a probability of 0.05 and 80% power on a two-tailed test with 90% confidence interval. A minimum number of 109 patients was enrolled in this study.

Baseline data

All selected patients in the study were subjected to the following:

1. Medical history including smoking index, level of asthma control using asthma control questionnaire (ACQ) score (Fig. 2), and inhaled corticosteroids (ICS) use.
2. Airway corticosteroid sensitivity was assessed by comparing post-bronchodilator FEV1 between a patient on inhaled corticosteroid for at least 3 months and patients who do not receive any form of corticosteroid. Also, sputum cytology and serum markers (serum level of periostin and eotaxin-2) were compared between a patient on inhaled corticosteroid for at least 3 months and patients who do not receive any form of corticosteroid. Subjects were receiving low 200-400, medium > 400-800, and high > 800 mcg daily doses of inhaled budesonide or equivalent according to GINA guideline [5].
3. Spirometry: Post-bronchodilator FEV1, FEV1/FVC, and FEF25-75 were measured. Moreover, TLC, RV/TLC, and Dlco were measured using pulmonary function analyzers (ZAN 300, NSPIRE HEALTH GMBH Co., Schlimpfhofer Str. 14, 97723 Oberthulba, Lower Franconia, Germany).
4. Sputum cytology: Collection of sputum samples: by instructing the patient to cough as deep as possible to expectorate about 5-10 ml in a sterile container usually early in the morning. Specimen transport/storage: Each specimen was individually collected in a sealed plastic bag with proper legible labeling and sterile containers. Sputum induction performed using hypertonic saline when needed [8].

Sputum samples were processed using the “pick and smear” technique of sputum processing.

This technique applied to fresh samples or samples prefixed in 50% alcohol. The selection of bloody or solid particles was critical in the correct processing of sputum. To select such particles, the sputum must be carefully inspected. This was done by pouring the specimen into a Petri dish and examining it against a black background. Excellent results were obtained by pouring sputum specimens on two or three thickness of brown-paper toweling. The paper toweling absorbed most of the fluid portion of the specimen and allowed the selection of particles. Sputum was often difficult to transfer to solid in small

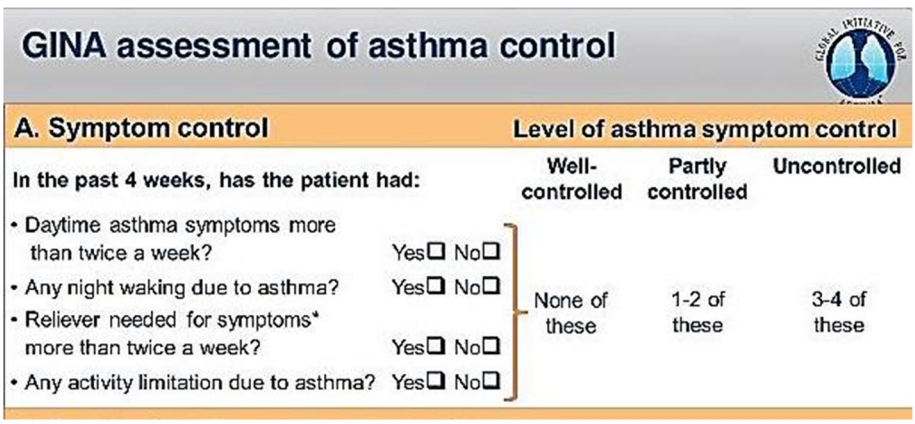

Fig. 2 Asthma control questionnaire [6]

amounts because of its viscous, ropy consistency. The use of two specially designed curette-type instruments, nasal curettes, or applicator, one on each hand, was required.

Any bloody, discolored, or solid particles, if present, were selected and placed in a small portion of each particle, not larger than the size of a small pea, on each of four plain slides. With a clean glass slide, the particle of sputum on each of the four slides was crushed, using a rotary motion. Then, with overlapping horizontal strokes, the material evenly over the slide was spread so that the final preparation is only slightly thicker than a blood smear. The prepared slides are immediately placed in a Coplin jar with 95% ethyl alcohol fixative, or its equivalent, making sure that the smeared surfaces remains separated by paper clips. In the absence of particles, a sputum sample from at least four different portions of the specimen must be smeared.

If cell blocks were to be prepared, the part of the specimen remaining after the preparation of smears was saved and proceeded.

5. Serum level of periostin was measured by commercially available human periostin (POSTN) ELISA kit [9] (SinoGeneClon Biotech Co., Ltd., Hangzhou, China) for the quantitative determination of human POSTN concentrations according to the manufacturer's specifications as the following.

Catalog no.: SG-10345.

Method type

Sandwich ELISA detection.

Product principle

The kit was for the quantitative level of human POSTN in the sample, adopted purified POSTN antibody to coat microtiter plate, made solid-phase antibody and then added POSTN to wells, combined POSTN antibody with labeled HRP to form antibody-antigen-enzyme-antibody complex, after washing completely, TMB substrate solution was added, TMB substrate became blue color at HRP enzyme-catalyzed, reaction was terminated by the addition of a stop solution, and the color change was measured at a wavelength of 450 nm. The concentration of POSTN in the samples was then determined by comparing the O.D. of the samples to the standard curve.

Sample collection

Blood samples were collected according to standard laboratory procedures. Venous blood samples of about 3 ml had been collected from patients under complete aseptic technique.

Specimen requirements

Serum-coagulation at room temperature for 10-20min, centrifuged at the speed of 2000-3000 rpm for 20 min. The supernatant was removed. Sample was centrifuged again if precipitation appeared. The samples assayed immediately or aliquot and stored at −20 °C or −80 °C. Repeated freeze-thaw cycles were avoided.

Reagent preparation

1. Wash buffer (1×): 20 ml of wash buffer concentrate (30×) was diluted into deionized or distilled water to prepare 600 ml of wash buffer (1×).
2. Standard: The standard was diluted: 50 μl standard dilution was pipetted in each tube. One hundred microliters (135 ng/ml) was pipetted in the fifth tube. And, 100 μl was taken out from the fifth of the five tubes into the fourth. Fifty microliters was pipetted from the fourth tube to the third tube and dilution series were produced as below. The undiluted standard served as the high standard (135 ng/ml). Sample diluent served as the zero standard (blank well) (0 ng/ml).

Assay procedure

Step 1: 50μl standard was pipetted to testing standard well, 40 μl sample dilution was pipetted to testing sample well, then 10 μl testing sample was added (sample final dilution is fivefold). Sample was pipetted to wells; the well wall did not touch as far as possible, and was mixed gently.
Step 2: Incubation: The well was covered with the adhesive strip provided, was incubated for 30 min at 37 °C.
Step 3: Configuration liquid: Wash solution was diluted 30-fold with distilled water.
Step 4: Washing: The adhesive strip was uncovered, the liquid was discarded, washing buffer was pipetted to every well, stilled for 30 s then drained, was repeated 5 times.
Step 5: Adding enzyme: 50 μl HRP-conjugate reagent was pipetted to each well, except blank well.
Step 6: Incubation: As in step 2.
Step 7: Washing: As in step 4.
Step 8: Color: 50 μl of chromogen solution A and chromogen solution B were pipetted to each well, incubated at 37 °C for 15 min away from light.
Step 9: The reaction stopping: 50 μl stop solution was pipetted to each well; the reaction was stopped (the blue change to yellow).
Step 10: Calculation: the blank well was taken as zero using Stat-Fax 303 plus ELISA Reader.

Absorbance was read at 450 nm after pipetting stop solution within 15 min.

Calculation of result

A standard curve was constructed by plotting the mean absorbance for each standard on the *Y*-axis against the concentration on the *X*-axis, and the best curve was drawn through the points on log-log graph paper. The absorbance value for each sample determined the corresponding concentration from the standard curve then multiplied by the dilution factor.

Serum level of Eotaxin-2

Was measured by commercially available human ELISA kit [10] (SinoGeneClon Biotech Co., Ltd., Hangzhou, China) according to the manufacturer's specifications. All the steps were the same as the previous kit (except the step of standard dilution).

The standard was diluted: 50 μl of standard dilution was pipetted in each tube. One hundred microliters of standard (1350 pg/ml) was pipetted in the fifth tube. And, 100 μl was taken out from the fifth five tube into the fourth. Fifty microliters was pipetted from the fourth tube to the third tube, and dilution series were produced as below. The undiluted standard served as the high standard (1350 pg/ml). Sample diluent served as the zero standard (blank well) (0 pg/ml).

Research outcome measures

Primary outcome measure was airway inhaled corticosteroid sensitivity. Secondary (subsidiary) were asthma control questionnaire (ACQ) score, spirometry, the proportion of eosinophils and neutrophils in sputum cytology, serum periostin, and serum eotaxin-2 level.

Statistical analysis

Data was collected and analyzed using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data were expressed in form of mean ± SD or median (range) while nominal data were expressed in form of frequency (percentage).

Chi^2 test was used to compare the nominal data of different groups while Student *t* test was used to compare continuous data of two groups while ANOVA test followed by post hoc analysis was used to compare continuous data of more than two groups. The level of confidence was kept at 95%, and hence the *P* value was considered significant if < 0.05.

Results

This study included 117 asthmatic patients (42 smokers, 30 ex-smokers, and 45 non-smokers) with a mean age of asthmatic smokers and non-smokers were significantly lower than ex-smokers (32.40 ± 8.22 and 28.93 ± 7.98 vs. 38.20 ± 7.76 years; $P < 0.001$, respectively). The majority of patients had no comorbidities with two asthmatic smokers who were diabetic with no statistical significance between groups. Three patients in non-smokers and four patients in the other groups had different comorbidities.

All patients had at least one previous exacerbation per year. The number of exacerbations, hospitalizations, and emergency room (ER) visit last year were higher with statistical significance in asthmatic smokers in comparison to ex-smokers and non-smokers, as shown in Table 1.

Table 2 and Fig. 3 showed that inhaled corticosteroid (ICS) therapy was significantly higher in asthmatic smokers and ex-smokers in comparison to non-smokers (26 (61.9%) and 17 (56.7%) vs. 10 (22.2%); ($P < 0.001$), respectively). Budesonide was the most frequently used inhaled corticosteroid therapy among the studied groups. The dose of inhaled corticosteroid was high in 30.9% of asthmatic smokers and 33.3% of ex-smokers. However, the dose of ICS was low in 22.2% of non-smokers.

As regard ICS response in asthmatic patients of different groups in correlation with clinical and laboratory parameters, Table 3 revealed that asthmatic smokers who received ICS and those who did not receive ICS had insignificant differences as regard ACQ, sputum cytology, pulmonary function test, serum eotaxin-2, and serum periostin. While it was noticed that asthmatic ex-smokers who received ICS had significantly higher post-bronchodilator FEV1 in comparison to those who did not receive ICS (88 ± 11.88 vs. 64.93 ± 25.83; ($P = 0.01$), respectively). However, asthmatic non-smokers who received ICS were significantly well controlled as regard ACQ in comparison to those who did not receive ICS. Moreover, they had significantly higher post-bronchodilator FEV1/FVC (86.1 ± 14.58 vs. 77 ± 14.23; $P = 0.04$), post-bronchodilator FEV1 (87.47 ± 23.5 vs. 65.9 ± 25.9; $P = 0.03$) and post-bronchodilator FEF25-75 (65.50 ± 38.59 vs. 40.22 ± 27.10; $P = 0.03$).

As regard effect of ICS on sputum eosinophils and neutrophils in all studied groups, there was decrease in sputum eosinophilic and neutrophilic count which was significantly lower in asthmatic non-smokers.

Discussion

In this study, asthmatic smokers were significantly higher in the number of exacerbations, hospitalizations, and emergency room (ER) visits last year in comparison to ex-smokers and non-smokers. Similarly, Thomson et al. [11] demonstrated that the number of hospital admissions in the last year were higher in smokers compared to ex-smokers and non-smokers without statistical significance.

Table 1 Baseline data of studied patients based on smoking state

	Smoker (*n* = 42)	Ex-smoker (*n* = 30)	None (*n* = 45)	*P*	*P*1	*P*2	*P*3
Age (years)	32.40 ± 8.22	38.20 ± 7.76	28.93 ± 7.98	**< 0.001**	**< 0.001**	**0.04**	**< 0.001**
Body mass index (kg/m^2)	27.69 ± 5.29	27.94 ± 4.76	25.80 ± 4.62	0.12	0.84	0.09	0.08
Duration of asthma (years)	10.09 ± 4.56	11.65 ± 4.28	7.42 ± 4.84	0.05	0.46	0.08	**0.02**
Allergic rhinitis	33 (78.6%)	33 (76.7%)	32 (71.1%)	0.70	0.65	0.09	0.09
Childhood asthma	21 (50%)	10 (33.3%)	14 (31.1%)	0.15	0.34	0.80	0.12
Family history	25 (59.5%)	16 (53.3%)	27 (60%)	0.82	0.76	0.12	0.08
Comorbidities				0.78	0.10	0.06	0.09
None	38 (90.5%)	26 (86.8%)	42 (93.4%)				
DM	2 (4.7%)	1 (3.3%)	1 (2.2%)				
HTN	1 (2.4%)	1 (3.3%)	0				
IHD	1 (2.4%)	1 (3.3%)	1 (2.2%)				
Hyperthyroidism	0	1 (3.3%)	1 (2.2%)				
Previous exacerbation/year	2 (1-20)	2 (1-7)	1 (1-5)	**0.01**	**0.02**	**< 0.001**	0.57
Previous hospitalization	5 (2-10)	1 (0-3)	1 (0-3)	**0.02**	**0.04**	**0.01**	0.42
Previous ER visit	5 (3-10)	4 (0-6)	4 (0-5)	**0.02**	**0.04**	**0.03**	0.10

Data expressed as frequency (percentage), mean (SD). *P* was significant if < 0.05. *P* compares between different three groups; *P*1 compares between smokers and ex-smokers; *P*2 compares between smokers and non-smokers; *P*3 compares between ex-smokers and non-smokers
ER emergency room

It is noteworthy that asthmatic smokers had no response to ICS as regard ACQ, sputum cytology, and pulmonary function test. However, asthmatic ex-smokers who received ICS had significantly higher post-bronchodilator FEV1 (88 ± 11.88 vs. 64.93 ± 25.83; P = 0.01) in comparison to those who did not receive ICS, with no significant clinical improvement as regard ACQ nor inflammatory profile difference while asthmatic non-smokers patients who received ICS were significantly well controlled as regard ACQ in comparison to those who did not receive ICS. Moreover, they had significantly higher post-bronchodilator FEV1/FVC (86.1 ± 14.58 vs. 77 ± 14.23; P = 0.04), post-bronchodilator FEV1 (87.47 ± 23.5 vs. 65.9 ± 25.9; P = 0.03), and post-bronchodilator FEF25-75 (65.50 ± 38.59 vs. 40.22 ± 27.10; P = 0.03). These results are consistent with the results of Arsovski et al. [12], who stated that after 6 weeks of treatment with inhaled fluticasone propionate with a dose of 250 mg twice per day (a total daily dose of 500 mg), a statistically significant positive effect for FEV1 (p < 0.05) was obtained from the therapy with fluticasone propionate among the group of asthmatic non-smokers

Table 2 Inhaled corticosteroid therapy among studied patients based on smoking status

	Smoker (*n* = 42)	Ex-smoker (*n* = 30)	None (*n* = 45)	*P*	*P*1	*P*2	*P*3
Inhaled corticosteroid therapy	26 (61.9%)	17 (56.7%)	10 (22.2%)	**< 0.001**	0.34	**< 0.001**	**< 0.001**
Type				**0.01**	0.19	**0.02**	**0.03**
Budesonide	21 (50%)	11 (36.7%)	6 (13.3%)				
Beclomethazone	5 (11.9%)	4 (13.3%)	3 (6.7%)				
Fluticasone	0	2 (6.7%)	0				
Ciclosonide	0	0	1 (2.2%)				
Duration (months)	23.36 ± 13.76	21.93 ± 14.26	20.58 ± 13.78	0.67	0.44	0.40	0.95
Dose (equivalent to budesonide, mcg/day)	625.45 ± 208.05	687.36 ± 230.09	566.67 ± 231.63	0.25	0.47	0.48	0.09
Category of doses				**0.02**	0.52	**0.03**	**0.04**
Low	6 (14.3%)	5 (16.7%)	10 (22.2%)				
Medium	7 (16.7%)	2 (6.7%)	0				
High	13 (30.9%)	10 (33.3%)	0				

Data expressed as frequency (percentage), mean (SD). *P* was significant if < 0.05. *P* compares between different three groups; *P*1 compares between smokers and ex-smokers; *P*2 compares between smokers and non-smokers; *P*3 compares between ex-smokers and non-smokers

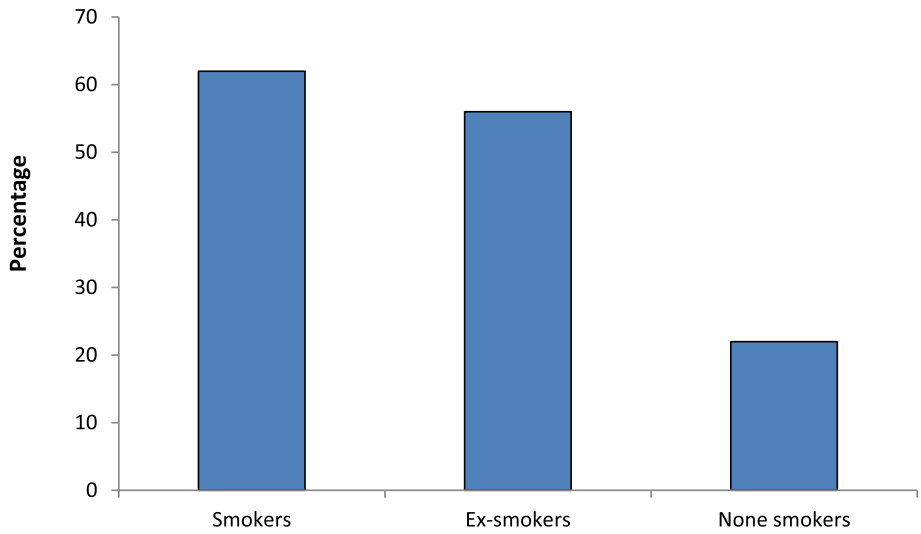

Fig. 3 Frequency of inhaled corticosteroid therapy among studied groups based on smoking status

compared to the effect of the therapy for the group of asthmatic smokers. Although the values of FEV1 given in percentage of improvement are small, they are satisfactory for initial spirometric values of patients with mild asthma.

Also, these results are near to the results of Lazarus et al. [13], who found that treatment with inhaled beclomethasone resulted in significant improvements from baseline in many outcomes of asthma control and airway function in non-smoking subjects with asthma. In contrast, they found that the only significant improvements from baseline in smokers were in morning peak expiratory flow (a.m. PEF) and sputum eosinophils. Moreover, these results are near to the results of Tomlinson et al. [14], who had shown that smokers with asthma had a reduced therapeutic response to inhaled corticosteroids over 3-month period compared with non-smokers.

In contrast to this study, O'Byrne et al. [15] reported that inhaled budesonide was equally effective in attenuating this decline in post-bronchodilator FEV1in smokers and non-smokers. The effects of smoking status and allocated treatment on pre-bronchodilator FEV1 were qualitatively similar to those on post-bronchodilator FEV1, although numerically somewhat larger. The effect of budesonide on changes in lung function was independent of smoking status, was based on placebo comparisons. The difference could be explained that their study studied the effect of ICS on mild persistent asthma who smoke and exclude moderate and severe asthma. Also, another limitation in their study was that the number of cigarettes smoked and the duration of smoking habit were not recorded for each patient. Thus, the decline in post-bronchodilator therapy FEV1 relative to the number of pack-years smoked could not be estimated.

There are several potential mechanisms by which smoking may induce insensitivity to corticosteroids in asthmatic patients. Experimental data suggest downregulation of histone deacetylase and/or enhanced neutrophil-mediated inflammation in smokers. Increased levels of tumor necrosis factor-α, or changes in the ratio of the glucocorticoid receptor (GR) isoform GR-α to GR-β [13].

As regards the effect of ICS on sputum inflammatory cells, the current study detected that sputum eosinophils and neutrophils in asthmatic non-smokers who received ICS were significantly lower in comparison to those who did not receive ICS (2.61 ± 1.35 vs. 8.75 ± 2.57; $P = 0.04$ and 7.15 ± 5.85 vs. 29.6 ± 6.91; $P = 0.01$, respectively). These results are consistent with the results found by Hoshino et al. [9], who found that the percentage of sputum eosinophils decreased significantly after treatment with ICS. Moreover, these results are near to Nader et al. [16] who concluded that beclomethasone influence on airway remodeling was mediated mainly via suppression of eosinophilic recruitment into the airways and reduction of interleukin-13 cytokine levels.

However, as regards the effect of ICS on serum periostin, it was detected that serum periostin had no statistically significant difference (slight decrease) in response to inhaled corticosteroids in all asthmatic patients (smokers, ex-smokers, and non-smokers). And among those taking inhaled corticosteroids, there was no significant correlation between the serum periostin concentrations and corticosteroid dose ($P = 0.21$) and duration ($P = 0.81$) in all asthmatic patients. These findings are consistent with the results reported by Thomson et al. [17] who found that the serum periostin concentration was no different comparing asthma patients who were taking or not taking inhaled

Table 3 Pulmonary function and sputum profile among studied groups based on ICS use

	Smokers			Ex-smokers			Non-smokers		
	Non ICS (*n* = 16)	ICS (*n* = 26)	*P* value	Non ICS (*n* = 13)	ICS (*n* = 17)	*P* value	No ICS (*n* = 35)	On ICS (*n* = 10)	*P* value
ACQ			0.23			0.38			**< 0.001**
Well controlled	1 (6.3%)	4 (15.4%)		0	3 (17.6%)		16 (45.7%)	9 (90%)	
Partly controlled	4 (25%)	7 (26.9%)		5 (38.5%)	7 (41.2%)		9 (25.7%)	1 (10%)	
Uncontrolled	11 (68.7%)	15 (57.7%)		8 (61.5%)	7 (41.2%)		10 (28.6%)	0	
Sputum cellularity									0.13
No	1 (6.2%)	4 (15.4%)	0.15	1 (7.7%)	1 (5.9%)	0.28	19 (54.3%)	4 (40%)	
Mild	6 (37.5%)	10 (38.5%)		5 (38.5%)	8 (47%)		10 (28.6%)	5 (50%)	
Moderate	0	1 (3.8%)		0	1 (5.9%)		2 (5.7%)	1 (10%)	
High	9 (56.3%)	11 (42.3%)		7 (53.8%)	7 (41.2%)		4 (11.4%)	0	
Alveolar macrophages	7 (44%)	12 (46.2%)	0.64	8 (61.5%)	7 (41.2%)	0.16	18 (51.4%)	5 (50%)	0.08
Eosinophils (%)	4.33 ± 1.95	2.99 ± 1.33	0.38	6.53 ± 2.13	4.73 ± 1.72	0.96	8.75 ± 2.57	2.61 ± 1.35	**0.04**
Neutrophils (%)	24.50 ± 4.93	17.83 ± 8.39	0.65	30.92 ± 3.60	11.57 ± 5.66	0.08	29.6 ± 6.91	7.15 ± 5.85	**0.01**
Histiocytes (%)	15.67 ± 6.08	18.33 ± 7.90	0.77	20.90 ± 3.85	14.73 ± 4.80	0.51	12.5 ± 2.43	11.14 ± 5.32	0.95
Lymphocytes (%)	12.50 ± 1.30	10.83 ± 1.48	0.12	16.36 ± 9.07	5.78 ± 4.26	0.19	8.33 ± 6.06	11.42 ± 3.21	0.66
Post-BD FEV1/FVC	69.36 ± 13.12	72.57 ± 11.32	0.45	68 ± 17.02	78.70 ± 9.45	0.08	77 ± 14.23	86.1 ± 12.58	**0.04**
Post-BD FEV-1	70.09 ± 15.78	73.23 ± 21.75	0.81	64.9 ± 25.83	88 ± 11.88	**0.01**	65.9 ± 25.9	87.47 ± 11.5	**0.03**
Post-BD FVC	91 ± 7.72	96.03 ± 4.94	0.68	79.77 ± 20.5	96 ± 3.93	**0.02**	83.2 ± 16.6	86.5 ± 11.55	0.73
Post-BD FEF_{25-75}	50.55 ± 39.61	55.33 ± 29.64	0.75	47.16 ± 11.49	55.09 ± 36.2	0.90	40.22 ± 27	65.50 ± 17.59	**0.03**
TLC (%)	176.12 ± 65.89	99.75 ± 28.3	0.31	141.2 ± 3.49	132.67 ± 4.58	0.40	104.63 ± 19.7	102.78 ± 25.31	0.84
RV/TLC (%)	49.22 ± 15.86	38.67 ± 16.36	0.23	45.75 ± 25.12	42.50 ± 7.93	0.86	47.85 ± 18.38	44.72 ± 16.23	0.87
DICo (%)	82 ± 24.86	92.50 ± 24.74	0.60	86.60 ± 27.30	98 ± 26	0.58	83.67 ± 11.58	91.25 ± 31.98	0.68
Periostin	18.03 ± 6.63	10.45 ± 9.65	0.23	16.34 ± 7.89	11.43 ± 1.41	0.08	21.61 ± 2.59	11.41 ± 4.74	0.12
Eotaxin-2	578.77 ± 98.7	437.28 ± 64.58	0.87	200 ± 66.67	152.94 ± 55.91	0.23	163.33 ± 51.11	108.62 ± 2.03	0.21

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05
ICS inhaled corticosteroid, *ACQ* asthma control questionnaire, *BD* bronchodilator, *FEV-1* forced expiratory volume-1, *FVC* forced vital capacity, *TLC* total lung capacity

corticosteroids; 78 (9, 750) vs. 34 (9, 364), $p = 0.647$. There was no difference among the smokers ($p = 0.676$) and never smokers ($p = 0.466$). Among those taking inhaled corticosteroids, there was no significant correlation between the corticosteroid dose and serum periostin concentrations in smokers ($p = 0.730$) and in never smokers ($p = 0.867$). In addition, this finding is near to the result of Matsumoto [18] who concluded that the effects of ICS on serum periostin levels appear to be minimal.

Strengths of this study

1. Relatively few studies had focused on the effects of smoking on outcomes of asthma control and airway inflammation in subjects with asthma.
2. Evaluation of the effectiveness of ICS was using multiple indicators of control.

Limitations of the current study

This study had some limitations. First, our study population includes only those patients who can perform acceptable and reproducible spirometry. Second, we could not obtain adequate sputum in all patients so only those patients who were able to produce a sputum sample of sufficient quality included. Third, patient adherence to ICS in this study was not monitored. Finally, it was better to follow up each patient individually after adherence to ICS for a certain period and compare the difference in patients' responses of the three groups.

Recommendations

Future studies are needed to examine the findings of this study prospectively as well as to investigate the utility of serum periostin and eotaxin-2 as biomarkers to predict responses to therapies, particularly biological agents, in different phenotypes of asthma including smokers with asthma.

Conclusions

Smokers with asthma have a lower response to the beneficial effects of inhaled corticosteroids (ICS). Smoking adversely affects the course and response to ICS therapy in asthma. There is currently no optimal drug therapy to

effectively treat airway inflammation in smokers with asthma; however, many potential targets for future therapies exist.

Abbreviations

ICS: Inhaled corticosteroid; ACQ: Asthma control questionnaire; FEV1: Forced expiratory volume in 1 s; FEV1/FVC: Forced expiratory volume in 1 s/forced vital capacity; FEF25-75: Forced mid-expiratory flow; GINA: The Global Initiative for Asthma; TLC: Total lung capacity; RV/TLC: Residual volume/total lung capacity; DlCo: Diffusing capacity; ER: Emergency room; a.m. PEF: Morning peak expiratory flow

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"Not applicable."

Authors' contributions

All the authors participated in conception and design. SFY and SA collected the data and samples. AFE, MAE, SFY, SA, MI, and MF were responsible for analysis and interpretation of data. MAE and SFY were responsible for drafting the article. AFE, MAE, and SFY revised it critically for final approval of the version to be published. All authors have read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the Local Ethics Committee of the Assiut University Hospital, the committee's reference number IRB no: 17200038 and was conducted in accordance with the previsions of the Declaration of Helsinki. Written informed consent was obtained from all the participants before enrollment.

Consent for publication

All the authors approved the manuscript for publication. Identifying images or other personal or clinical details of participants is "Not Applicable." Consent for publication from the participants is "Not Applicable."

Competing interests

The authors declare that they have no competing interests.

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