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A comparative study evaluating C-reactive protein, sputum eosinophils and forced expiratory volume in one second in obese and nonobese asthmatics

Abstract

Introduction: Asthma and obesity are considered inflammatory disorders. Inflammatory markers — sputum eosinophils, C-reactive protein (CRP) and the forced expiratory volume in one second (FEV_1) were analysed to find their association in obese asthmatics and compared with their asthma control test (ACT) to understand these parameters in this phenotype.

Material and methods: After completing the asthma control test (ACT), the CRP, FEV_1 and sputum eosinophils of sixty asthmatics were compared to find the association of them in obese and nonobese asthmatics and contrasted with their ACT. The data were analysed using IBM SPSS V20.0, Mann-Whitney U test (non-parametric test), Pearson's correlation coefficient and Fisher's exact test.

Results: We found significant differences for CRP ($P = 0.001$) and sputum eosinophils ($P = 0.001$) between obese and nonobese asthmatics, both higher in obese asthmatics and with a significant association with body mass index (BMI) ($P < 0.05$). The FEV_1 levels were independent of the BMI levels of asthmatics. There was a significant correlation between the CRP and sputum eosinophils (0.52, $P = 0.001$) for all asthmatics. There was no significant correlation between FEV_1 and sputum eosinophils (nonobese $P = 0.120$, obese $P = 0.388$) and between FEV_1 and CRP (obese $P = 0.423$, nonobese $P = 0.358$) in both obese and nonobese asthmatics. Obesity had an association ($P = 0.001$) with ACT scores (≤ 19).

Conclusions: Sputum eosinophils and CRP were raised in obese asthmatics and had a positive association with BMI. Obese asthmatics had a poorer subjective asthma control than nonobese asthmatics despite FEV_1 being independent of the BMI levels. Measuring the systemic inflammatory markers could help in additional interventions in reducing systemic inflammation and thus possibly facilitating better symptom control.

Key words: C-reactive protein, sputum eosinophils, FEV_1, obese asthmatics, systemic inflammation

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Introduction

Asthma is a syndrome characterised by recurrent episodic airway obstruction, airway inflammation and bronchial hyper-responsiveness. It is a syndrome with a variety of phenotypes, where various precipitating factors result in clinical, physiological and pathological manifestations. The main pathogenesis of asthma is the infiltration of inflammatory cells such as eosinophils, basophils, and CD4 + lymphocytes in the airways [1, 2].

Obesity is also considered an inflammatory disorder conveyed by various systemic inflammatory mediators like C-reactive protein (CRP) that leads to an increase in circulating levels of the pro-inflammatory cytokines. CRP is also raised in various systemic inflammations such as diabetes, cardiovascular diseases, collagen vascular diseases, malignancies, and also obesity [3–5]. Various studies have shown that severe asthma is more prevalent in obese patients as compared with patients with normal body mass index (BMI) and that BMI is positively associated with asthma severity [6]. Also, BMI correlates positively with the level of asthma control, with more severe asthmatics having a higher BMI than

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those with milder asthma [7, 8]. Thus, obesity seems to be related with asthma severity, but the mechanisms responsible for this relationship are not yet clarified.

There is growing evidence that asthma and obesity are strongly associated with each other and can alter each other's status [9]. Also, the inflammatory cells, sputum eosinophils and interleukin-5 play a major role in airway inflammation in asthmatics, more so in obese asthmatics who are already in a pro-inflammatory state [10]. Evidence of neutrophilic inflammation of the airways in obese asthmatics has also been documented [11], but the association between the non-neutrophilic airway inflammation in obesity, the systemic inflammation and the lung function remains poorly understood, especially in different phenotypes and endotypes of asthma. As the treatment of asthma has evolved from the airway obstruction-based approach to a tailored-endotype and phenotype-based approach, especially in special subsets of asthma like the obese phenotypes, it helps to know the relationship between the inflammatory markers both systemic (CRP) and airway (sputum eosinophils), with the forced expiratory volume in one second (FEV_1) in this regard.

As our understanding of various subtypes of asthma has evolved over years, here we try to evaluate the obese asthmatic subtype and the inflammatory markers associated with both the airway (sputum eosinophils) and systemic marker (CRP), and correlate them with their lung function (FEV_1) and compare the same with nonobese asthmatics. This might help us to understand the systemic inflammatory component of asthma, specifically concerning the obese asthmatic phenotype and the markers associated with it. Correlating these inflammatory markers with the patient's subjective control of symptoms through the asthma control test (ACT) could give us a better understanding of the roles these inflammatory markers play in the symptom control.

The purpose of this cross-sectional study was to evaluate the systemic inflammation using CRP, airway inflammation by measuring sputum eosinophils and the measure of lung function by FEV_1 in obese and nonobese asthmatics, compare and correlate these parameters between the obese and nonobese groups. We also try to ascertain whether there is a significant association between the inflammatory markers (sputum eosinophils, CRP) amongst each other and with FEV_1 and to compare BMI with the asthma control test (ACT) scores.

Materials and methods

Sixty asthmatic patients who presented to the outpatient department of Respiratory Medicine, in Sree Balaji Medical College and Hospital, Chennai. were recruited for the study from 2018 to 2019. We aimed to compare and evaluate CRP, FEV_1 and sputum eosinophils in obese and nonobese asthmatics and to find the association of CRP, FEV_1, and sputum eosinophils among each other and compare BMI with the asthma control test scores (ACT) [12].

Patients with a primary diagnosis of asthma according to the Global Initiative for Asthma (GINA) guidelines, 18 years of age or older were included in this study. Individuals with nonreversible airway obstruction on spirometry (< 12% change in FEV_1) who were unable to do spirometry due to a history of myocardial infarction, congestive heart failure, coronary artery disease, who had a history of smoking, with known comorbidities like diabetes, cardiovascular diseases, collagen vascular diseases and malignancies were excluded from the study.

All the patients who satisfied the inclusion criteria, filled up the asthma control test and were later told to do pulmonary function test — spirometry, serum CRP and sputum sample after deep coughing in a sterile container. Then sputum quality was assessed using both macroscopic and microscopic criteria [13]. Sputum was stained with eosin and haematoxylin and analysed using microscopy to determine the count of eosinophils expressed in percentage, and counts ≥ 3 % was considered to be high [14], BMI ≥ 30 kg/m^2 were considered obese, and CRP > 1 mg/dL was considered high-risk. The ACT is a patient-completed questionnaire for individuals above 12 years of age and consists of five items evaluating the preceding 4 weeks (limitation of activities, shortness of breath, awakenings at night, use of reliever medication and patient's perception of asthma control). Each question has five response options, resulting in scores of 1–5. The sum of all scores yields the total ACT score, a score of less than equal to 19 indicates poorly controlled asthma, and a score greater than equal to 20 indicates good asthma control, the maximum being 25. All the participants had forced expiratory volume 1 second/functional vital capacity (FEV_1/FVC) < 70% with post-bronchodilator reversibility FEV_1 > 12% on spirometry.

Statistical analysis: A total of 60 patients were included in the study. The data were analysed using IBM SPSS V 20.0. Mann-Whitney

U test (non-parametric test) was performed for comparing outcome variables between obese and nonobese groups, Pearson's correlation coefficient was computed to measure the association of the outcome variables amongst each other and Fisher's exact test was used to find the association of BMI with the asthma control test score. P-value < 0.05 was considered to be statistically significant.

Results

There were a total of 60 subjects. Among them, the number of males were 22 (37%) and females were 38 (63%). The mean age was 41.48 (SD = 10.98). All of the participants were classified as obese (BMI ≥ 30) and nonobese (BMI < 30) (Table 1). Among the 60 subjects, 32 were obese and 28 were nonobese (Table 1).

We found statistically significant differences in CRP (P = 0.001) and sputum eosinophils (P = 0.001) between obese and nonobese asthmatics (Table 1). We noted that the median CRP was higher, 2 mg/dL for obese asthmatics compared to 1 mg/dl for nonobese asthmatics (Table 1, Figure 1). Also, the same trend was reflected in median sputum eosinophils, being 6% for obese asthmatics and 2% for nonobese asthmatics (Table 1, Figure 2). However, we did not find any significant difference in FEV_1 between obese and nonobese asthmatics (P = 0.882) (Table 1).

Among the associations between the parameters themselves (Table 2), we observed that there was a significant correlation between the CRP and sputum eosinophils (0.52, P = 0.001) for all asthmatics (Figure 3). We found no significant correlation between FEV_1 and sputum eosinophils (nonobese P = 0.120, obese P = 0.388) and also between FEV_1 and CRP (obese P = 0.423, nonobese P = 0.358) in both obese and nonobese asthmatics. Comparing the BMI with the asthma control test scores (Table 3), we noticed that asthma was not controlled (ACT scores ≤ 19) for 94% of obese asthmatics as compared to only 25% for nonobese asthmatics, and there was a significant association (P = 0.001) between obesity (BMI) and ACT scores.

Table 1. Comparison of outcome variables between obese and nonobese asthmatics. Values presented as median with interquartile range in parenthesis. *Mann-Whitney-u non-parametric test; P value < 0.05 — statistically significant

Outcome	Non-obese (N = 28)	Obese (N = 32)	*P* value*
CRP	1 (0–1)	2 (1–4)	0.001
FEV_1	60 (59–70)	64 (55–71)	0.882
Sputum eosinophils	2 (2–3)	6 (4–7)	0.001

CRP — C-reactive protein; FEV_1 — forced expiratory volume in one second

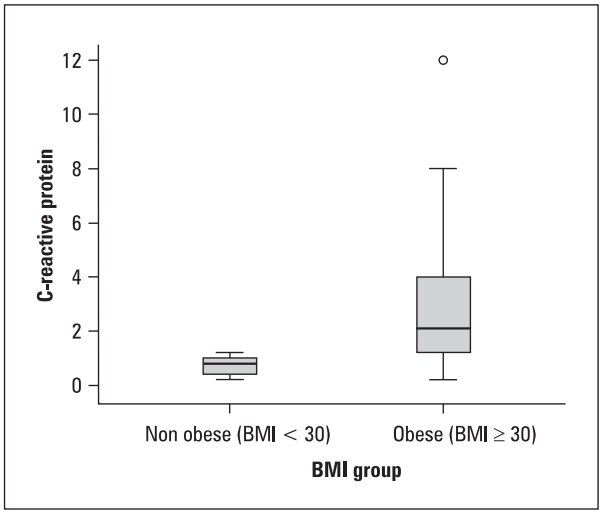

Figure 1. Comparison of C-reactive protein between obese and nonobese asthmatics. BMI — body mass index

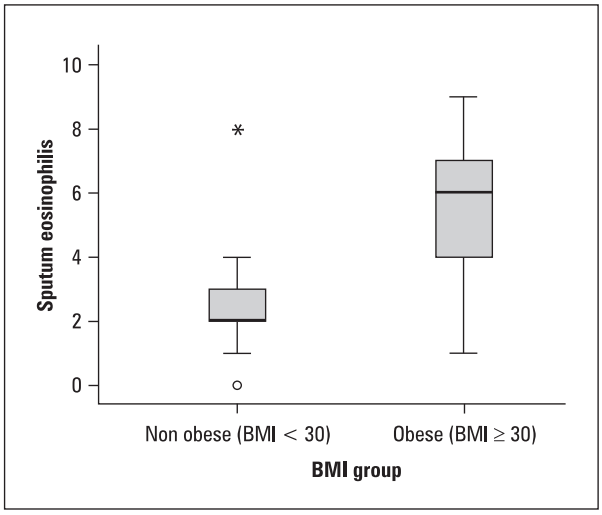

Figure 2. Comparison of sputum eosinophils between obese and nonobese asthmatics

Table 2. Association between outcomes in obese and nonobese asthmatics

		Outcome	FEV_1	Sputum eosinophils
Non-obese (N = 28)	Correlation*	CRP	0.069	0.080
	P value		0.358	0.337
	Correlation*	FEV_1		-0.221
	P value			0.120
Obese (N = 32)	Correlation*	CRP	-0.037	0.301
	P value		0.423	0.053
	Correlation*	FEV_1		-0.054
	P value			0.388
All samples (N = 60)	Correlation*	CRP	-0.012	0.520
	P value		0.464	0.001
	Correlation*	FEV_1		-0.082
	P value			0.268

*Pearson correlation coefficient. P value < 0.05 — statistically significant. CRP — C-reactive protein; FEV1 — forced expiratory volume in one second

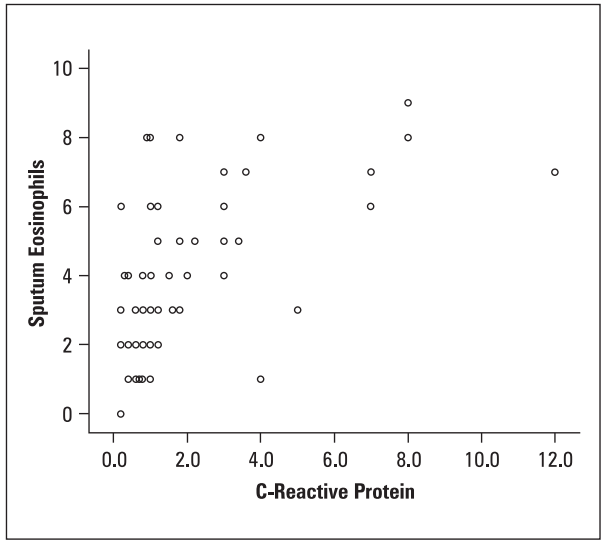

Figure 3. Association between C-reactive protein and sputum eosinophils in all asthmatics

Discussion

This study aimed to compare the CRP, FEV_1 and sputum eosinophils in obese and nonobese asthmatics and to ascertain whether there is an association between the groups. We also sought to find a link between the inflammatory markers — CRP and sputum eosinophils and FEV_1, and also among each other in asthmatics and correlate it with asthma control test scores. To the best of our knowledge, this study is one of the very few studies done to compare the various inflammatory markers in both obese and nonobese asthmatics and probably the first study to try to find an association between the inflammatory markers themselves and with the BMI. We also tried to correlate the inflammatory markers with the self-perception of symptom control through the asthma control test.

With our data, we found that median CRP and sputum eosinophils were higher in obese asthmatics than in nonobese asthmatics. Also, CRP and sputum eosinophils had a positive association with BMI. However, the FEV_1 did not correlate positively with BMI. Our findings were in concordance with the findings of Van Veen *et al.* regarding FEV_1 that has not decreased in obese asthmatics and has not shown a significant difference between obese and nonobese asthmatics [15]. Interestingly, our study was in contrast to the other finding reported in the same study wherein the authors showed that obese asthmatics do not have more airway inflammation as compared with nonobese asthmatics. But in our study, sputum eosinophils and CRP were also found to be higher in obese asthmatics and had a positive correlation with each other for all asthmatics.

Obese asthmatics had a significant association with asthma control test scores, predominant number of obese asthmatics (94%) had uncontrolled ACT (score ≤ 19). Even if the FEV_1 was independent of the BMI levels, our patients who were obese had an increased perception of symptoms reflected through the poor asthma control scores of less than equal to 19. An increase in systemic inflammation in obesity has been well described [16]. It has been suggested that high levels of pro-inflammatory molecules released from adipose tissue into the systemic circulation could

Table 3. Association between body mass index (BMI) and asthma control test (ACT)

	Non-obese (BMI < 30)	Obese (BMI ≥ 30)	P-value*
Asthma not controlled (ACT ≤ 19)	7 (25)	30 (94)	**0.001**
Asthma controlled (ACT > 19)	21 (75)	2 (6)	

Numbers with percentage in parenthesis. *Fisher's exact test; P value < 0.05 — statistically significant

contribute to the airway inflammation, thus increasing the prevalence and poor asthma control in obese asthmatics [17]. In our study, CRP levels were found to be elevated in obese asthmatics and this probably explains that this pro-inflammatory state could lead to increased perception of symptoms. The inflammatory markers (CRP and sputum eosinophils) were independent of the FEV_1 in all asthmatics, and thus perception of breathlessness reflected by the poor asthma control test scores (ACT ≤ 19) in these obese phenotypes of asthmatics could indeed be caused by the systemic inflammation. Many other studies have also demonstrated a positive correlation between elevated CRP levels and asthma control, respiratory impairment and bronchial hyper-reactivity [18–21].

Among the associations between the inflammatory mediators themselves, the CRP and sputum eosinophils showed a positive correlation in all asthmatics. Our study was in agreement with a similar study by Abdelsadek *et al.* who showed a positive correlation with CRP and sputum eosinophils in asthmatics [22]. In this study, however, the BMI wasn't correlated with the inflammatory markers. The mechanism of airway inflammation is complex in obese asthmatics. It can be mediated through various inflammatory mediators like interleukin (IL)-4, IL-5, IL-13, inflammatory cells like eosinophils, mast cells and basophils to name a few apart from the possible overlay of systemic inflammation. Non-eosinophilic inflammation and systemic inflammation could also play an important role in airway inflammation in obese asthmatics.

Obesity has been demonstrated to be a risk factor for asthma and is associated with an increased prevalence of asthma symptoms [23, 24]. But this, whether it is because of systemic inflammation, airway constriction or the change in dynamics of respiration and the restrictive defect or a contributory factor of both, needs to be investigated.

As the asthma treatment guidelines are evolving from a symptom-based approach to a tailored approach, it will be wise to optimise the treatment based on various phenotypes and endotypes, and thus probably reducing an impending exacerbation. Interestingly, many studies have previously shown that treating the airway inflammation led to better asthma control and thus, in turn, reduced hospitalisations and fatal events [25], and if the treatment strategy is aimed at keeping sputum eosinophils low, patients might have fewer asthma exacerbations [26]. Since elevated CRP is often associated with accelerated lung function decline [27], aiming at the treatment based on markers of inflammation both the airway and systemic inflammation is a more scientific and rational approach than treating the physiological effects caused by it, which is particularly relevant, especially in obese asthmatics. These obese asthmatics who have an overlay of systemic inflammation could also be phenotyped as a separate entity. In our study, the CRP and sputum eosinophils were higher in obese asthmatics, which suggests concordance between these biomarkers; and similarly to treating the airway inflammation, whether treating the systemic inflammation in these obese phenotypes leads to better asthma control, needs to be examined. Thus, the measure of systemic inflammatory markers in obese asthmatics with poor disease and symptom control plays an important role, and this should help to ascertain the systemic mediator's role and thus help to devise a treatment plan for these subsets of patients. This should ideally include rigorous weight management plans apart from pharmacological interventions in obese asthmatics which aim at reducing the systemic inflammatory mediators like the CRP levels. This might yield a better asthma control wherein the contributors of breathlessness can also be caused by restrictive lung defect in obesity. Apart from their airway inflammation, measuring the systemic inflammation adds a definitive value in difficult to treat obese asthmatics with poor symptom control. It is hoped that these results will help to understand the systemic inflammation of the obese phenotype of asthma and provide better asthma management. Serial measurements of CRP, sputum eosinophils and FEV_1, additional interventions and follow-ups

could have given us more insights into these parameters in different disease states and during various levels of asthma controls.

Conclusions

Thus, the inflammatory markers sputum eosinophils and CRP were raised in obese asthmatics and had a positive association with BMI. Obese asthmatics had a poorer subjective asthma control than the nonobese asthmatics despite FEV_1 being independent of the BMI levels. Measuring the systemic inflammatory markers in obese asthmatics who do not have adequate subjective symptom control reflected by uncontrolled ACT scores, could add a definitive value and possibly help in additional interventions aimed at reducing systemic inflammation and facilitating better symptom control.

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Conflict of interest

None declared.

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