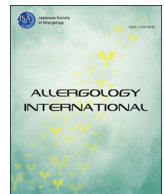




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Letter to the Editor

Obesity-related systemic oxidative stress: An important factor of poor asthma control

Dear Editor:

Obesity has recently been recognised as one of the factors of poor asthma control. However, the mechanistic basis for asthma in the obese has not been sufficiently clarified yet. Obesity is known to induce systemic oxidative stress through various mechanisms, such as chronic inflammation, endothelial dysfunction, and mitochondrial dysfunction.¹ Oxidative stress induces propagation of airway inflammation and resistance to steroid therapy.² The facts imply that oxidative stress might be involved in the poor asthma control in obese subjects. However, previous reports regarding the association between obesity-related systemic oxidative stress and asthma are controversial.^{3–5} An important limitation of these reports is that data showing the association between asthma control statuses or the frequency of exacerbations and obesity-related oxidative stress is lacking; only the associations among asthma morbidity, obesity, and oxidative stress were investigated.

Our objective was to evaluate the potential effect of systemic oxidative stress on acute exacerbations in obese asthmatic patients. For this purpose, we investigated the association between serum markers and clinical parameters, including the frequency of severe acute exacerbations in obese and non-obese asthmatic patients.

Patients were recruited from the outpatient clinic of the Department of Allergy and Respiratory Medicine at the Fraternity Memorial Hospital. Inclusion criteria were patients who satisfied the following conditions: 1) had asthma diagnosed according the Global Initiative for Asthma (GINA) guidelines; 2) were receiving GINA therapy step 4 or 5; 3) had received regular medication for at least 1 year prior to enrolment; 4) had no systemic or pulmonary infection within 4 weeks of enrolment; and 5) had no exacerbations requiring the administration of systemic corticosteroids within 4 weeks of enrolment. Severe acute exacerbations were defined in an official statement of American Thoracic Society (ATS) and European Respiratory Society (ERS).⁶ Briefly, it should include at least one of the following criteria: 1) Use of systemic corticosteroids for at least 3 days; or 2) A hospitalization or unscheduled visit due to asthma, requiring systemic corticosteroids. Clinical data including the frequency of severe acute exacerbations (FSE) per year (between one year before collection of serum sample and at the time of the collection) were collected from the medical records. Serum samples were collected from the patients. Serum leptin and malondialdehyde (MDA, an oxidative stress marker) levels were measured by ELISA (R&D system, Minneapolis, MN, USA) and thio-barbituric acid reactive substances assay kit (Cayman, Ann Arbor, MI, USA), respectively. The enrolled asthmatic patients were

divided into 2 groups according to BMI (the obesity group [OB] = BMI $\geq$ 25 and the non-obesity group [NOB] = BMI < 25) based on the criteria of Japan Society for the Study of Obesity, and the parameters were compared between the groups. This cut-off was chosen because a BMI of 25 kg/m² is the optimal cut-off for maximising the sensitivity and specificity for obesity-related disorders in Japanese people.⁷ Statistical analyses were performed using IBM SPSS Statistics version 23. Comparisons of 2 groups of data (continuous variables or discrete variables) were performed by Mann–Whitney U test. The non-parametric Spearman correlation was used to evaluate correlations between two parameters. Fisher's exact test was used for comparisons of proportions in categorical variables. This study was reviewed and approved by the research ethics committee of the Fraternity Memorial Hospital.

Table 1

Demographic data, spirometry and serum marker of enrolled patients.

	Non-obesity	Obesity	<i>p</i>
<i>n</i>	33	16	
Body mass index (kg/m ²)	22.1 $\pm$ 1.9	28.4 $\pm$ 2.9	<0.0001
Age (yr)	52 $\pm$ 14	58 $\pm$ 17	0.337
Smokers (Ex & Current)	7 (25%)	3 (19%)	0.724
Sex (F:M)	28:5	11:5	0.261
Pack-year	4.1 $\pm$ 8.9	4.9 $\pm$ 16.0	0.446
Duration of asthma (year)	20 $\pm$ 12	17 $\pm$ 13	0.370
Asthma therapy and Control			
GINA therapy step (4:5)	26 (79%):7 (21%)	11 (69%):5 (31%)	0.492
High dose ICS	17 (52%)	10 (63%)	0.549
Daily use of oral corticosteroids	3 (9%)	3 (19%)	0.377
Frequency of severe acute exacerbations (/year)	0 (0–1)	2 (0–6)	0.038
Spirometry			
FVC (L)	2.53 $\pm$ 0.80	2.58 $\pm$ 0.93	0.907
%FVC (%)	83.2 $\pm$ 18.1	83.8 $\pm$ 13.8	0.881
FEV ₁ (L)	2.12 $\pm$ 0.71	2.13 $\pm$ 0.82	0.991
%FEV ₁ (%)	82.6 $\pm$ 22.5	85.1 $\pm$ 15.7	0.773
FEV ₁ /FVC (%)	82.4 $\pm$ 9.9	81.8 $\pm$ 7.0	0.579
%PEF (%)	78.6 $\pm$ 21.6	81.9 $\pm$ 20.6	0.741
%FEF ₅₀ (%)	76.8 $\pm$ 42.4	83.4 $\pm$ 36.6	0.515
%FEF ₇₅ (%)	71.1 $\pm$ 43.7	64.7 $\pm$ 30.5	1.000
Serum markers			
Serum Leptin (ng/mL)	16.9 $\pm$ 11.3	27.3 $\pm$ 12.1	0.007
Serum MDA (μ M)	2.8 $\pm$ 0.7	3.3 $\pm$ 0.8	0.034

Data are given as 'mean $\pm$ SD' or as 'number (%)'. Frequency of severe acute exacerbations data is given as 'median (interquartile range)'.

GINA, Global Initiative for Asthma; ICS, Inhaled corticosteroids; FVC, Forced vital capacity; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow; FEF₅₀, forced expiratory flow at 50% of the vital capacity; FEF₇₅, forced expiratory flow at 75% of the vital capacity; MDA, malondialdehyde.

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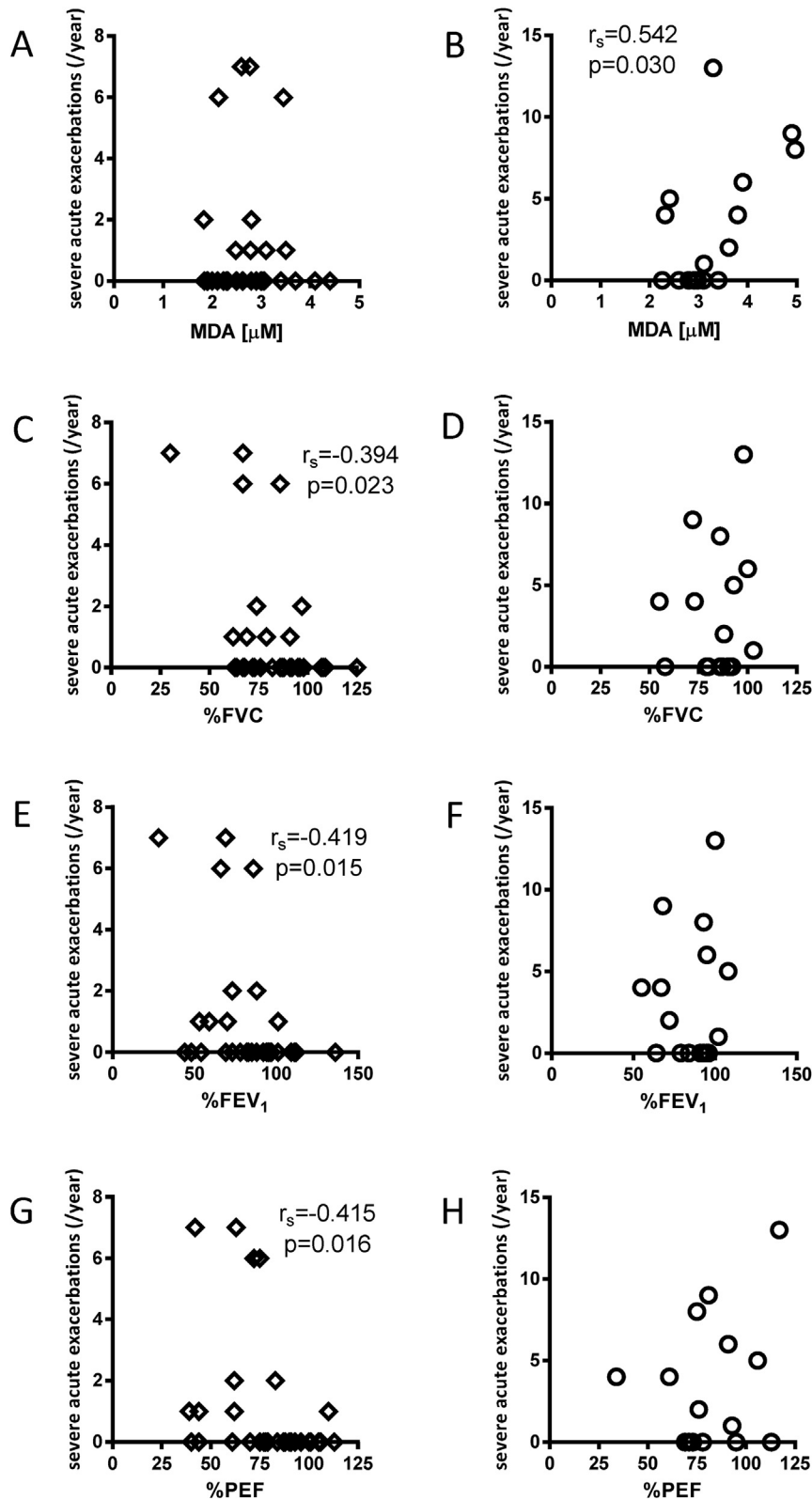


Fig. 1. Correlations between the frequency of severe acute exacerbations and clinical and serum parameters. The correlation analysis was performed in each group (obese asthma group and non-obese asthma group). Graphs showing (A) FSE vs serum MDA in NOB (n = 33); (B) FSE vs serum MDA in OB (n = 16); (C) FSE vs %FVC in NOB (n = 33); (D) FSE vs %FVC in OB (n = 16); (E) FSE vs %FEV₁ in NOB (n = 33); (F) FSE vs %FEV₁ in OB (n = 16); (G) FSE vs %PEF in NOB (n = 33); and (H) FSE vs %PEF in OB (n = 16). FSE, frequency of severe acute exacerbations; MDA, malondialdehyde; FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; PEF, peak expiratory flow.

Sixteen asthmatic patients with obesity and 33 asthmatic patients without obesity were enrolled. There were no significant differences in age, duration of asthma, pack-year, or spirometry data between OB and NOB (Table 1). Serum leptin and MDA were significantly higher in OB than those in NOB (Table 1). BMI significantly correlated with FSE ($r_s = 0.389$, $p = 0.006$), serum MDA ($r_s = 0.324$, $p = 0.023$), and serum leptin ($r_s = 0.515$, $p = 0.001$). Next, we carried out correlation analyses in each group, OB and NOB. There was a significant positive correlation between the FSE and serum MDA in OB ($r_s = 0.542$, $p = 0.030$) (Fig. 1B), but not in NOB ($r_s = -0.017$, $p = 0.925$) (Fig. 1A). In contrast, the FSE was significantly associated with poor lung function levels in NOB [%FVC, $r_s = -0.394$, $p = 0.023$ (Fig. 1C); %FEV₁, $r_s = -0.419$, $p = 0.015$ (Fig. 1E); and %PEF, $r_s = -0.415$, $p = 0.016$ (Fig. 1G)], but not in OB [$r_s = 0.152$, $p = 0.574$ (Fig. 1D); $r_s = 0.115$, $p = 0.670$ (Fig. 1F), and $r_s = 0.195$, $p = 0.469$ (Fig. 1H)], respectively. No significant correlations were detected between the FSE and serum leptin in both OB ($r_s = 0.346$, $p = 0.190$) and NOB ($r_s = 0.049$, $p = 0.785$).

In this study, we have found that the factors associated with FSE are different between obese and non-obese asthmatic patients. FSE and pulmonary function tests in NOB were significantly inversely correlated, which is commonly observed in asthmatic patients in general. However, FSE and pulmonary function tests did not correlate in OB. FSE significantly correlated with the oxidative stress marker in OB only. These results suggest that systemic oxidative stress in obese asthmatic patients is a stronger facilitator of acute exacerbations than a decline in pulmonary function. Elevated systemic oxidative stress in obesity is known to induce more severe airway inflammation and resistance to steroid therapy. This condition potentially causes poor asthma control, even in patients with good pulmonary function, resulting in frequent severe acute exacerbations. Systemic oxidative stress seems to play a significant role in severe acute exacerbations only in obese asthmatic patients.

The strength of our study is that FSE was used as an index of poor asthma control and the association with systemic oxidative stress was investigated and evaluated independently in OB and NOB. In addition, the definition of severe acute exacerbation used in this study was in the official statements of ATS and ERS. Previous studies of this association did not consider asthma control status or the frequency of exacerbations, and their results were controversial. Collectively, obesity-related systemic oxidative stress associates with poor asthma control, but is not sure to associate with asthma morbidity.

Recently, *in vitro* experiments showed that leptin induced oxidative stress.⁸ However, serum leptin did not correlate with FSE ($p = 0.190$) or serum MDA ($p = 0.934$) in OB in this study whereas serum MDA correlated with FSE (Fig. 1B). These findings suggest that oxidative stress, which affects FSE, does not originate from elevated serum leptin but likely originates from various mechanisms related to obesity.

Leptin has also been reported to induce inflammatory cytokines *in vitro*⁹ and may associate with the pathogenesis of asthma with obesity. However, there was no significant correlation between serum leptin and FSE in this study. The discrepancy was probably caused by leptin resistance in obese subjects.¹⁰ While leptin acts to suppress appetite and mediate weight loss, obese subjects maintain their weight and high food intake despite the high serum leptin level as a result of resistance to the effects of leptin.¹⁰ Obese

subjects are also speculated to be resistant to the pro-inflammatory action of leptin; therefore, leptin only partially affects obese asthmatic patients even with high serum leptin levels.

The limitation of this study was that the sample size was small. The conclusions, therefore, may be affected. However, the data provide important information for future large-scale studies.

In conclusion, obesity-related systemic oxidative stress have close association with acute exacerbation of asthma in obese subjects, therefore it seem to play important roles in poor asthma control in obese asthmatic patients. Decreasing oxidative stress and/or argumentation of anti-oxidants may be beneficial for the management of obesity-related severe asthma.

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Conflict of interest

The authors have no conflict of interest to declare.

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