

# Impact of obesity on adipokines, inflammatory cytokines and clinical symptoms control in asthmatic subjects

## Abstract

**Background:** Recently, bronchial asthma and obesity are major global health issues.

**Objective:** The aim of this study was to measure the relationship between adipokines, inflammatory cytokines and clinical symptoms in obese asthmatic Saudi patients.

**Subjects and Methods:** Two hundred Saudi patients of both sex; their age mean was  $40.17 \pm 8.36$  year with bronchial asthma. According to body mass index (BMI), participants were classified into two equal groups. Group (A) included one hundred obese asthmatic patients and group (B) included one hundred asthmatic patients with normal body weight.

**Results:** The mean value of tumor necrotic factor-alpha (TNF- $\alpha$ ), Interleukin-6 (IL-6), leptin and resistin were significantly elevated in obese asthmatic patients when compared with non-obese asthmatic patients. However, the mean value of Asthma Control Test (ACT) and adiponectin was significantly lower in obese asthmatic patients when compared with non-obese asthmatic patients. The Pearson's correlation coefficients test for the relationship between body mass index & TNF- $\alpha$ , IL-6, leptin and resistin showed a strong direct relationship, while there was a strong inverse relationship between BMI, ACT and adiponectin among obese asthmatic patients.

**Conclusion:** There is a strong association between inflammatory cytokines, adipokines, asthma control test and body mass index among obese asthmatic patients. Therefore, life style modification intervention is essential for modulation of biochemical and clinical symptoms in obese asthmatic patients.

**Keywords:** systemic inflammation, adipokines, asthma clinical test, obesity, bronchial asthma

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**Abbreviations:** ACT, asthma control test; FVC, forced vital capacity; BMI, body mass index; TNF, tumor necrotic factor

## Introduction

Bronchial asthma and obesity are common medical problems as there are more than 300 million patients with bronchial asthma<sup>1,2</sup> and 2 billion obese and overweight subjects worldwide.<sup>3</sup> However, about 36% of American subjects were obese in 2009-2010.<sup>4</sup> In this regard, association between obesity and asthma reduce responsiveness to steroid therapy, increase exacerbation of asthma and reduce control of asthma.<sup>5-8</sup> Cardiovascular disorders are common among patients with bronchial asthma.<sup>9,10</sup> The association between cardiovascular disease and asthma is stronger in women than men.<sup>11</sup> However, systemic inflammation increase the risk for cardiovascular disorders in bronchial asthma.<sup>12</sup> Moreover, neutrophilic airway inflammation, increased resistance for corticosteroids and increased morbidity are criteria for an association between obesity and asthma.<sup>13-15</sup>

Adipokines play an important role in regulation of different physiological body functions.<sup>16</sup> There was an association between asthma, adiponectin and leptin.<sup>17</sup> However, there is an interest in study of role of adipose tissue in development of asthma in obesity as adipose tissue is considered as an active endocrine organ that elaborating adipokines, hormones and cytokines which regulate immune and metabolic response.<sup>18</sup> The aim of this study was to measure the relationship between Adipokines, inflammatory cytokines and clinical symptoms in obese asthmatic Saudi patients.

## Subjects and methods

Two hundred Saudi patients of both sex; their age mean was  $40.17 \pm 8.36$  year with bronchial asthma in a controlled state according to GINA.<sup>1</sup> Participants were selected from outpatients of the Internal Medicine Department, King Abdulaziz University Hospital, Jeddah, Saudi Arabia. According to body mass index (BMI), participants were classified into two equal groups. Group (A) included one hundred obese asthmatic patients and group (B) included one hundred asthmatic patients with normal body weight. Exclusion criteria included individuals with infectious disease, cardiovascular, rheumatic, malignancy, liver and kidney disorders, breast-feeding and pregnant women, and individuals with obesity due to secondary factors were excluded from the study. In addition, bronchial asthma patients who were receiving systemic steroids in the preceding 4 weeks were also excluded. The local ethics committee, Faculty of Applied Medical Sciences at King Abdulaziz University, approved the study and all patients gave their informed consent.

## Methods

### Evaluated parameters

- Measurement of inflammatory and Adipokines markers serum level: After a 10 hours overnight fast, venous blood samples were drawn to determine serum level of tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6) (GE Healthcare Amersham, Biotrak Easy ELISA) which was utilized the quantitative sandwich enzyme immunoassay technique. However, ELISA was used to measure serum level of adiponectin and leptin (Origenium Laboratories, Finland). Moreover, serum level of resistin was measured

by ELISA using kits (resistin: Rapidbio, West Hills, CA, USA; CK-18: PEVIVA, Alexis, Grunwald, Germany).

- B. Lung Function Testing: Spirometer (CPFS/D Spirometer; MedGraphics, St. Paul, Minn., USA) was used to measure lung function test that included the forced vital capacity (FVC), forced expiratory volume in the first second (FEV<sub>1</sub>), FEV<sub>1</sub>/FVC ratio and forced expiratory flow during the middle half of the FVC maneuver (FEF<sub>25-75</sub>%).
- C. Asthma Control Assessment: Italian version of the asthma control test (ACT) is a reliable assessment tool for control of asthma over time.<sup>19</sup> Participants answer five questions, each question has to be answered by five-point scale, and then the total scores of the five questions range from 0-25. However, if the total score obtained 19 or less this indicate poorly controlled asthma.<sup>20,21</sup>

### Statistical analysis

SPSS (Chicago, IL, USA) version 23 was used in statistical analysis of this study. However, differences between both groups was detected by independent t-test and the Pearson or Spearman rank correlation test was used to measurement of the relationship between continuous variables included asthma control test and (TNF- $\alpha$ , IL-6, leptin, adiponectin, resistin).

## Results

The demographic and clinical characteristics of the subjects are shown in Table 1. There was no significant age, gender, disease duration and hemoglobin difference between the obese and normal-weight asthmatic patients. However body mass index (BMI), waist hip ratio, waist circumference, forced vital capacity (FVC), forced expiratory volume in the first second (FEV<sub>1</sub>), ratio between forced expiratory volume in the first second and forced vital capacity (FEV<sub>1</sub>/FVC) and forced expiratory flow during the middle half of the FVC maneuver (FEF<sub>25-75</sub>%) were significantly different between the obese and normal-weight asthmatic patients.

**Table 1** Baseline and spirometry characteristics of all participants

Parameters	Obese asthmatics	Non-obese asthmatics
Age (year)	38.94 $\pm$ 10.52	40.12 $\pm$ 9.76
Gender (F/M)	27/23	26/24
Disease duration ( year)	13.24 $\pm$ 5.28	11.87 $\pm$ 5.63
Body mass index(kg/m <sup>2</sup> )	34.61 $\pm$ 4.13*	22.16 $\pm$ 2.88
Waist hip ratio	0.92 $\pm$ 0.26*	0.81 $\pm$ 0.22
Hemoglobin (gm/dl)	13.25 $\pm$ 1.39	13.64 $\pm$ 1.47
FVC (L)	2.86 $\pm$ 1.14*	3.91 $\pm$ 1.32
FEV <sub>1</sub> (L)	1.93 $\pm$ 0.81*	2.72 $\pm$ 1.25
FEV <sub>1</sub> /FVC (%)	65.41 $\pm$ 7.55*	67.53 $\pm$ 7.96
FEF <sub>25-75</sub> % (L/s)	1.43 $\pm$ 1.42*	2.75 $\pm$ 1.61

FVC: forced vital capacity; FEV<sub>1</sub>: forced expiratory volume in the first second; FEV<sub>1</sub>/FVC: ratio between forced expiratory volume in the first second and forced vital capacity; FEF<sub>25-75</sub>: forced expiratory flow during the middle half of the FVC maneuver; \*: indicates a significant difference between the two groups, P<0.05.

The mean value of tumor necrotic factor-alpha (TNF- $\alpha$ ), Interleukin-6 (IL-6), leptin and resistin were significantly elevated in obese asthmatic patients when compared with non-obese asthmatic patients. However, the mean value of Asthma Control Test (ACT) and adiponectin was significantly lower in obese asthmatic patients when compared with non-obese asthmatic patients (Table 2). The Pearson's correlation coefficients test for the relationship between body mass index & TNF- $\alpha$ , IL-6, leptin and resistin showed a strong direct relationship, while there was a strong inverse relationship between BMI & ACT and adiponectin among obese asthmatic patients (Table 3).

**Table 2** Mean value and significance of IL-6, TNF- $\alpha$ , ACT, leptin, adiponectin and resistin of group (A)

Parameters	Pearson's value (R)
TNF- $\alpha$ (pg/ml)	0.721*
IL-6 (pg/ml)	0.642*
ACT (0-25)	- 0.617*
Leptin (ng/ml)	0.593*
Adiponectin ( $\mu$ g/ml)	- 0.715*
Resistin(ng/mL)	0.585*

ACT, asthma control test; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrotic factor-alpha; \*, indicates a significant difference between the two groups, P<0.05.

**Table 3** Shows the Pearson's correlation coefficients test value and the relationship between the BMI and IL-6, TNF- $\alpha$ , ACT, leptin, adiponectin and resistin group (A)

Parameters	Pearson's value (R)
TNF- $\alpha$ (pg/ml)	0.721*
IL-6 (pg/ml)	0.642*
ACT (0-25)	- 0.617*
Leptin (ng/ml)	0.593*
Adiponectin ( $\mu$ g/ml)	- 0.715*
Resistin(ng/mL)	0.585*

ACT, asthma control test; IL-6, interleukin-6; TNF- $\alpha$ , tumor necrotic factor-alpha; significance was calculated by spearman or pearson correlation (2-tailed); \*p<0.05; r, correlation coefficient.

## Discussion

There is an association between the risk for asthma and obesity as both of them are linked epidemiologically.<sup>22-24</sup> Hence, this study was done to confirm the interrelationship of inflammatory cytokines, leptin and adiponectin serum levels with asthma and obesity. All asthmatic patients included in this study were in a controlled state according to GINA.<sup>1</sup> Furthermore, pulmonary function of the studied population showed a lower FVC, FEV<sub>1</sub> and FEF<sub>25-75</sub>% of obese asthmatic group than none obese asthmatic group, these findings agreed with Canoz et al.<sup>25</sup> and Salome et al.<sup>26</sup> stated that increased value of BMI adversely affect lung volumes.<sup>25,26</sup> In addition, King et al.<sup>27</sup> and Jones et al.<sup>28</sup> reported that reduction in lung volume and narrowing of airways are associated with increased BMI in young adults with bronchial asthma.<sup>27,28</sup>

Our study showed a higher leptin and resistin serum levels in obese asthmatics compared to none obese asthmatics and in obese control compared to none obese control and there was a highly significant statistical relationship between BMI and leptin serum level with a direct correlation between serum leptin and BMI. The adipose tissue is considered a major source for many cytokines and Adipokines as leptin, resistin, adiponectin, this is in harmony with several previous studies found an association between BMI and serum leptin in patients with asthma.<sup>29-32</sup> Moreover, our study showed that serum adiponectin levels were significantly lower among obese asthmatics compared to non-obese asthmatics and negatively correlated with BMI and this is in agreement with Sood et al.<sup>33</sup> and Nagel et al.<sup>34</sup> reported an inverse relationship between serum adiponectin and risk of asthma.<sup>33,34</sup> However, Abdul Wahab et al.<sup>13</sup> found serum adiponectin is lower in obese -than none obese asthmatics in their studied population with a highly significant statistical association between BMI and adiponectin.<sup>13</sup> However, there are limited studies about the level of resistin in asthma as Larochelle et al.<sup>35</sup> proved a direct relationship between serum resistin and severity of asthma,<sup>35</sup> in the other hand Kim et al.<sup>36</sup> found a protective effect of resistin against asthma among children.<sup>36</sup> Finally, Silswal et al.<sup>37</sup> reported that inflammatory cytokines enhanced expression of in asthmatic patients.<sup>37</sup>

Regarding the inflammatory cytokines, this study proved that obese asthmatic patients had higher levels of serum TNF- $\alpha$ , IL-6 than non-obese asthmatic patients as both asthma and obesity had an inflammatory pathway as increased adipose tissue mass lead to increase release of pro-inflammatory cytokines that exaggerate severity of asthma. Previous studies proved that pro-inflammatory mediators increased in asthma<sup>38</sup> and other studies found significantly increased levels of IL-6, TNF- $\alpha$  and leptin in the obese than non-obese asthmatic patients.<sup>39,40</sup>

Concerning the asthma control, this study proved that asthma control was worse among obese asthmatic patients than non-obese asthmatic patients, however several studies provided mixed results regarding the relationship between BMI and asthma control as Kilic et al.<sup>41</sup> and Kattan et al.<sup>42</sup> found poor control of asthma among obese asthmatic women assessed with Asthma Control Test.<sup>41,42</sup> However, Rodrigo et al.<sup>43</sup> and Taylor et al.<sup>44</sup> reported increased hospitalization rates among obese than non-obese asthmatic patients.<sup>43,44</sup> While, Dixon et al.<sup>45</sup> and Peters-Golden et al.<sup>46</sup> stated that obese patients had poor response to asthma control medications.<sup>45,46</sup> Moreover, Lavoie et al.<sup>47</sup> proved poor quality of life and poor control of asthma symptoms among patients with higher BMI.<sup>47</sup> Moreover, obesity is among factors impairing asthma symptoms control and poor response to treatment as obesity tend to make control of asthma more difficult which proved by studies proved that all of these complains improved following weight-control intervention among obese asthmatic patients.<sup>48-50</sup>

The clinical implication of the findings in this study indicates that life style modification intervention is essential for modulation of biochemical and clinical symptoms in obese asthmatic patients.

## Conclusion

There is a strong association between inflammatory cytokines, adipokines, asthma control test and BMI among obese asthmatic patients.

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None.

## Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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## References

- Global Initiative for Asthma. Global strategy for asthma management and prevention 2006. GINA report; 2012.
- Barros R, Moreira P, Padrao P, et al. 90 Obesity increases the prevalence and the incidence of asthma and worsens asthma severity. *Clinical Nutrition*. 2016;36(4):1068–1074.
- Shore SA. Obesity and asthma: location. *Eur Respir J*. 2013;41(4):253–254.
- Ogden CL, Carroll MD, Kit BK, et al. Prevalence of obesity among adults: United States, 2011–2012. *NCHS Data Brief*. 2013;131:1–8.
- Lugogo NL, Monica K, Dixon AE. Does obesity produce a distinct asthma phenotype? *J Appl Physiol*. 2010;108(3):729–734.
- Sutherland ER. Linking obesity and asthma. *Ann N Y Acad Sci*. 2014;1311:31–41.
- Granell R, Henderson AJ, Evans DM, et al. Effects of BMI, fat mass, and lean mass on asthma in childhood: a Mendelian randomization study. *PLoS Med*. 2014;11:e1001669.
- Scott HA, Gibson PG, Garg ML, et al. Airway inflammation is augmented by obesity and fatty acids in asthma. *Eur Respir J*. 2011;38(3):594–602.
- Appleton SL, Ruffin RE, Wilson DH, et al. Asthma is associated with cardiovascular disease in a representative population sample. *Obes Res Clin Pract*. 2008;2(2):91–99.
- Cazzola M, Calzetta L, Bettoncelli G, et al. Cardiovascular disease in asthma and COPD: a population-based retrospective cross-sectional study. *Respir Med*. 2012;106(2):249–256.
- Lee HM, Truong ST, Wong ND. Association of adult-onset asthma with specific cardiovascular conditions. *Respir Med*. 2012;106(7):948–953.
- Gudbjartsson DF, Bjornsdottir US, Halapi E, et al. Sequence variants affecting eosinophil numbers associate with asthma and myocardial infarction. *Nat Genet*. 2009;41(3):342–347.
- Abdul Wahab A, Maarafiya MM, Soliman A, et al. Serum leptin and adiponectin levels in obese and non-obese asthmatic school children in relation to asthma control. *J Allergy*. 2013.
- Carpio C, Villasante C, Galera R, et al. Systemic inflammation and higher perception of dyspnea mimicking asthma in obese subjects. *J Allergy Clin Immunol*. 2016;137(3):718–726.
- Agrawal A, Prakash YS. Obesity, metabolic syndrome, and airway disease: a bioenergetic problem? *Immunol Allergy Clin North Am*. 2014;34(4):785–796.
- Assad NA, Sood A. Leptin, adiponectin and pulmonary diseases. *Biochimie*. 2012;94(10):2180–2189.
- Bianco A, Nigro E, Monaco ML, et al. The burden of obesity in asthma and COPD: Role of adiponectin. *Pulmonary Pharmacology & Therapeutics*. 2017;43:20–25.
- Lumeng CN, Saltiel AR. Inflammatory links between obesity and metabolic disease. *J Clin Invest*. 2011;121(6):2111–2117.
- Quanjer PH, Tammeling GJ, Cotes JE, et al. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl*. 1993;16:5–40.
- Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113(1):59–65.
- Halbert RJ, Tinkelman DG, Globe DR, et al. Measuring asthma control is the first step to patient management: a literature review. *J Asthma*. 2009;46(7):659–664.
- Cazzola M, Segreti A, Calzetta L, et al. Comorbidities of asthma: current knowledge and future research needs. *Curr Opin Pulm Med*. 2013;19(1):36–41.
- Ford ES. The epidemiology of obesity and asthma. *J Allergy Clin Immunol*. 2005;115(5):897–909.
- Gershon AS, Wang C, Guan J, et al. Burden of comorbidity in individuals with asthma. *Thorax*. 2010;65(7):612–618.
- Canoz M, Erdenen F, Uzun H, et al. The relationship of inflammatory cytokines with asthma and obesity. *Clin Invest Med*. 2008;31(6):E373–E379.
- Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol*. 2010;108(1):206–211.
- King GG, Brown NJ, Diba C, et al. The effects of body weight on airway calibre. *Eur Respir J*. 2005;25(5):896–901.
- Jones RL, Nzekwu MM. The effects of body mass index on lung volumes. *Chest*. 2006;130(3):827–833.

29. Shah NR, Braverman ER. Measuring adiposity in patients: the utility of body mass index (BMI), percent body fat, and leptin. *PLoS One*. 2012;7(4):e333308.
30. Bastard JP, Jardel C, Bruckert E, et al. Elevated levels of interleukin 6 are reduced in serum and subcutaneous adipose tissue of obese women after weight loss. *J Clin Endocrinol Metab*. 2000;85(9):3338–3342.
31. McLachlan CR, Poulton R, Car G, et al. Adiposity, asthma and airway inflammation. *J Allergy Clin Immunol*. 2007;119(3):634–639.
32. Claude SF, Cheryl MS. Asthma and obesity: a known association but unknown mechanism. *Respirology*. 2012;17(3):412–421.
33. Sood A, Cui X, Qualls C, et al. Association between asthma and serum adiponectin concentration in women. *Thorax*. 2008;63(10):877–882.
34. Nagel G, Koenig W, Rapp K, et al. Associations of adipokines with asthma, rhinoconjunctivitis, and eczema in German schoolchildren. *Pediatr Allergy Immunol*. 2009;20(1):81–88.
35. Larochelle J, Freiler J, Dice J, et al. Plasma resistin levels in asthmatics as a marker of disease state. *J Asthma*. 2007;44(7):509–513.
36. Kim KW, Shin YH, Lee KE, et al. Relationship between adipokines and manifestations of childhood asthma. *Pediatr Allergy Immunol*. 2008;19(6):535–540.
37. Silswal N, Singh AK, Aruna B, et al. Human resistin stimulates the pro-inflammatory cytokines TNF-alpha and IL-12 in macrophages by NF-kappaB-dependent pathway. *Biochem Biophys Res Commun*. 2005;334(4):1092–1101.
38. Shore SA, Fredberg JJ. Obesity, smooth muscle, and airway hyper responsiveness. *J Allergy Clin Immunol*. 2005;115(5):925–927.
39. Sutherland TJ, Cowan JO, Young S, et al. The association between obesity and asthma. *Am J Respir Crit Care Med*. 2008;178(5):469–475.
40. Dixon EA, Shade DM, Cohen RI, et al. Effect of obesity on clinical presentation and response to treatment in asthma. *Journal of Asthma*. 2006;43(7):553–558.
41. Kilic H, Oguzulgen IK, Bakir F, et al. Asthma in obese women: outcomes and factors involved. *J Investig Allergol Clin Immunol*. 2011;21(4):290–296.
42. Kattan M, Kumar R, Bloomberg GR, et al. Asthma control, adiposity, and adipokines among inner city adolescents. *J Allergy Clin Immunol*. 2010;125(3):584–592.
43. Rodrigo GJ, Plaza V. Body mass index and response to emergency department treatment in adults with severe asthma exacerbations: a prospective cohort study. *Chest*. 2007;132(5):1513–1519.
44. Taylor B, Mannino D, Brown C, et al. Body mass index and asthma severity in the National Asthma Survey. *Thorax*. 2008;63(1):14–20.
45. Dixon AE, Shade DM, Cohen RI, et al. Effect of obesity on clinical presentation and response to treatment in asthma. *J Asthma*. 2006;43(7):553–558.
46. Peters-Golden M, Swern A, Bird SS, et al. Influence of body mass index in the response to asthma controller agents. *Eur Respir J*. 2006;27(3):495–503.
47. Lavoie KL, Bacon SL, Labrecque M, et al. Higher BMI is associated with worse asthma control and quality of life but not asthma severity. *Respir Med*. 2006;100(4):648–657.
48. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2014.
49. Boulet LP. Asthma and obesity. *Clin Exp Allergy*. 2013;43(1):8–21.
50. McGinley B, Punjabi NM. Obesity, metabolic abnormalities, and asthma: establishing causal links. *Am J Respir Crit Care Med*. 2011;183(4):424–425.