Study on the Effect of Metabolic Syndrome on Bronchial Asthma

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ABSTRACT

BACKGROUND
Asthma (synonymous with bronchial asthma) as a disease is known since ancient Egyptian times but despite tremendous efforts its clear pathology has not been elicited. Asthma globally causes considerable morbidity and mortality i.e. as of 2009; 300 million people worldwide were affected by asthma leading to approximately 250,000 deaths per year. Metabolic syndrome is one of the co-morbidities in asthma patients. Here in this study we are going to focus on metabolic syndrome as a comorbid condition of asthma. We assessed the effect of metabolic syndrome in asthma severity.

METHODS
100 patients were studied in the age group of 18-65 years. Patients who refused to give consent and those with other co-morbidities were excluded from the study. Spirometry was performed. Patients’ blood pressure, weight, height, waist circumference were measured. Patient’s lipid profile, blood sugar levels, FEV1, FVC, PEFR were measured and recorded. Levels of asthma control were assessed by Asthma Control Test and Asthma Severity was classified into intermittent, mild persistent, moderate persistent and severe persistent using symptoms and PEFR.

RESULTS
In our study out of 100 patients, 36 were males and 64 were females. The metabolic syndrome was found in 38 patients. Those without MS had a better asthma control than those with MS. Only 5.3% asthmatics with MS had well controlled asthma when compared with 67.7% asthmatics without MS (p-value 0.000). Asthmatics with MS had mild persistent asthma in 36.8% while those without MS were 35.5% (p-value 0.000). Moderate persistent asthma was present in 50% of AS with MS while only 6.5% asthmatics without MS had moderate persistent asthma. Severe persistent asthma was present in none of the asthmatics without MS and 13.2% AS with MS had severe asthma.

CONCLUSIONS
The prevalence of metabolic syndrome is high among bronchial asthma patients. In the study no significant association between presence of metabolic syndrome and pulmonary function tests was established in asthma patients. Significant association was found between presence of metabolic syndrome and asthma severity and asthma control (p value <0.001). Almost half of the asthmatics with metabolic syndrome had partly controlled asthma with moderate persistent severity.

KEYWORDS
Asthma, Metabolic Syndrome, Obesity, Pulmonary Function Test, Asthma Control Test, Asthma Severity Scale
Asthma globally causes considerable morbidity and mortality i.e. as of 2009, 300 million people worldwide were affected by asthma leading to approximately 250,000 deaths per year. Asthma is a chronic inflammatory disorder of the airways. Chronically inflamed airways are hyper responsive; they become obstructed and airflow is limited (by bronchoconstriction, mucus plugs, and increased inflammation) when airways are exposed to various risk factors. Asthma causes recurring episodes of wheezing, breathlessness, chest tightness, and coughing, particularly at night or in the early morning. Factors that influence the risk of asthma can be divided into those that cause the development of asthma and those that trigger asthma symptoms i.e. host factors and environment factors.

| Host Factors | Environment Factors |
|--------------|---------------------|
| Genes predisposing to atopy | Indoor: domestic mites, furred animals, cockroach allergen, fungi, molds, yeast. |
| Genes predisposing to airway hyper responsiveness. | Outdoor: pollens, fungi, molds, yeast. |
| Obesity | Infections (viral), Tobacco smoke (active/passive) |
| Sex | Occupational sensitizers |
| Allergies | Outdoor/indoor air pollution, Diet |

*Table 1. Factors Influencing the Development and Expression of Asthma*

Airway inflammation has a central role in the pathophysiology of asthma which involves an interaction of multiple cell types and inflammatory mediators with the airways that eventually results in the characteristic pathophysiological features of the disease: bronchial inflammation and airflow limitation that result in recurrent episodes of cough, wheeze, and shortness of breath. In asthma, the dominant feature leading to clinical symptoms is airway narrowing and interference with airflow. Allergen induced acute bronchoconstriction results from an IgE-dependent release of mediators from mast cells that include histamine, tryptase, leukotrienes, and prostaglandins that directly contact airway smooth muscle 23. In a seminal study, Dunnill described the classical findings in patients dying of acute severe asthma. The airways were characteristically blocked by viscous, tenacious mucus within an acutely distended lung parenchyma; gross emphysema was absent. Many airways were completely occluded by mucous plugging, composed of eosinophils and epithelial cells.

Airway inflammation in asthma mainly involves eosinophils, CD4 T-lymphocytes and mast cells, with eosinophilia infiltration being the most prominent feature. The airway wall of patients with asthma is characterized by increased smooth muscle mass, mucous gland hypertrophy and vascular congestion leading to a thickened airway wall and markedly reduced airway caliber. The increase in smooth muscle mass may be due to several factors, including proliferation of smooth muscle induced by inflammatory mediators, cytokines and growth factors. The increase in smooth muscle mass may be due to several factors, including proliferation of smooth muscle induced by inflammatory mediators, cytokines and growth factors.

In a study in Department of Paediatrics, University of Chieti, Chieti, Italy, it has been postulated that insulin resistance is a state in which a given amount of insulin produces a subnormal biological response. In particular, it is characterized by a decrease in the ability of insulin to stimulate the use of glucose by muscles and adipose tissue and to suppress hepatic glucose production and output.

Myoung-Sook Bae et al conducted a study at the Eulji General Hospital Health Center between January 2, 2008 and August 13, 2008. The study concluded that men with metabolic syndrome tended to experience lung function impairment. The more metabolic syndrome diagnostic criteria factors the male patients had, the more severe their pulmonary function tended to decline. In women, components of metabolic syndrome were not associated with pulmonary function impairment. Although in women,
waist circumference, triglyceride and high-density lipoprotein cholesterol were associated with pulmonary function change. Thuesen BH et al in a study done in 2009 concluded that insulin resistance was associated with incident wheezing (OR 1.87, 95% CI) and asthma-like symptoms (OR 1.61, 95% CI). The effect of insulin resistance was stronger than that of obesity and was independent of sex. A study shows that obese patients with the metabolic syndrome have a higher proportion of blood monocytes and eosinophils and a lower FEV1/VPC ratio, indicating airway obstruction. Proving the hypothesis that the presence of the metabolic syndrome could play a role in lung function impairment, through the induction of systemic inflammation, in particular mediated by blood eosinophils.

We wanted to determine the prevalence of metabolic syndrome among bronchial asthma patients and compare the asthma severity, control and pulmonary functions amongst those with metabolic syndrome and those without metabolic syndrome.

METHODS

This is a single centre based cross-sectional study. Patients aged between 18-65 years with bronchial asthma. Patients refusing to give consent, newly diagnosed cases of asthma, age <18 and >65 years, patients with Chronic Obstructive Pulmonary Disease (COPD), Interstitial Lung Disease (ILD), pleural disease, chest wall disorders & neuromuscular disorders, pregnant patients, patients with endocrinal comorbidity other than diabetes like hypo/hyper thyroidism, Cushing syndrome etc., pulmonary hypereosinophilia, chronic smokers and critically ill patients were excluded from the study.

Diagnosis of asthma was made in accordance with prescribed guidelines of GINA (Global Initiative for Asthma)²- Asthma is diagnosed on the basis of patient’s symptoms and medical history. Signs and symptoms – wheezing, chest tightness, worsening of symptoms at night, seasonal worsening of symptoms, family history of asthma, symptoms responding to anti-asthma therapy, patients colds ‘go to chest’ or take more than 10 days to clear up.

Spirometry to measure airflow limitation and its reversibility to establish diagnosis of asthma. An increase in FEV1 of >12% and >200 ml after administration of a bronchodilator indicates reversible airflow limitation is consistent with asthma. PEF measures an improvement of 60L/min after inhalation of a bronchodilator, or diurnal variation in PEF of more than 20% suggests a diagnosis of asthma. Levels of Asthma Control was Assessed by Asthma Control Test. Asthma severity is classified into intermittent, mild persistent, moderate persistent and severe persistent using symptoms and PFR.

According to the new IDF (The New International Diabetes Federation Definition (2006))³ definition, for a person to be defined as having the Metabolic Syndrome they must have:

Central obesity (defined as waist circumference 90 cm for Asiad men and 80 cm for Asiad women, with ethnicity specific values for other groups) plus any two of the following four factors: 1. Raised TG level: > 150 mg/dL (1.7 mmol/L), or specific treatment for this lipid abnormality. 2. Reduced HDL cholesterol: <40 mg/dL (0.9 mmol/L) in males and < 50 mg/dL (1.1 mmol/L) in females, or specific treatment for this lipid abnormality. 3. Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg, or treatment of previously diagnosed hypertension. 4. Raised fasting plasma glucose (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes.

| Characteristics | Controlled | Partly Controlled | Uncontrolled |
|-----------------|------------|------------------|-------------|
| Day time symptoms | None/less than twice a week | More than twice/week | Three or more Features of Partly controlled asthma. |
| Limitation of activities | None | Any | |
| Nocturnal symptoms | None | Any | |
| Need for reliever | None/less than twice a week | More than twice/week | |
| Lung function | Normal | <80% predicted | |

Table 2. Summary of Asthma Control Test

| Symptoms/Day | Symptoms/Night | PEF /FEV1 |
|--------------|----------------|-----------|
| Intermittent | <1 time/week | Asymptomatic & PEF normal in between attacks. | <=2 times a month | >=80% |
| Mild persistent | >1 time a week but <3 times/day. Attacks may affect activity. | >=2times a month | =>80% |
| Moderate persistent | Daily. Attacks affect activity. | >1 times/week | 60-80% |
| Severe persistent | Continuous limited physical activity. | frequent | <=60% |

Table 3. Summary of Asthma Severity²

RESULTS

The age range was between 18 and 65 years with a mean age of 37.41 ± 11.55 years. The mean age of males and females were 40.83 ± 12.93 and 35.48 ± 10.33.

Demographic Characteristics

The mean age of patients with metabolic syndrome was 38.92 ± 10.87 and those without metabolic syndrome was 36.48 ± 11.95. The mean age difference among asthmatics with and without MS was not significant (p-value 0.309). The prevalence of obesity among asthmatics according to BMI was 79%. Asthmatics with normal BMI (18-25) were 21. There were 42 obese asthmatics with BMI 25-30. The asthmatics with severe obesity with BMI >30 (p-value 0.010) were 37. The mean BMI of asthmatics with metabolic syndrome was 30.40 ± 4.25 while those without metabolic syndrome was 26.67 ± 4.32. This difference in BMI with relation to MS was significant with p-value 0.000. The prevalence of diabetes was 23% with 23 asthmatics having diabetes. Hypertension was present in 17% of the

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asthmatics. Allergic rhinitis, allergic sinusitis, allergic conjunctivitis and atopic dermatitis was present in 1%, 3%, 1% and 1% respectively. Out of 23 diabetic asthmatics, 15 (39.5%) were having metabolic syndrome while 8 (12.9%) were not having MS, this difference was significant with p-value 0.002. Out of 17 hypertensive asthmatics, 11 (28.9%) were having metabolic syndrome while 6 (9.7%) were without MS, this difference in HTN was not significant (p-value 0.13). Mean fasting blood sugar was 118.16 ± 28.64 mg/dl in AS with MS while mean fasting blood sugar in asthmatics without MS was 82.48 ± 9.81 mg/dl, with significant p-value of 0.000. Mean abdominal girth was 93.39 ± 10.39 cm in AS with MS and those without MS had mean of 66.16 ± 14.84 cm (p-value 0.000). Mean systolic and diastolic blood pressure was 132.39 ± 8.24 mmHg and 85.00 ± 5.9 mmHg in patients with AS and MS. Mean blood pressure in AS without MS was 119.89 ± 8.78 mmHg systolic and 75.76 ± 5.66 mmHg diastolic, with significant difference (p-value 0.000). The mean high density lipoprotein cholesterol (HDL), mean triglyceride (TG) and low density lipoprotein cholesterol (LDL) of the patients were 36.34 ± 5.85, 163.11 ± 42.17 and 105.16 ± 28.36 in AS with MS. The mean HDL, TG and LDL in patients with AS without MS were 49.52 ± 8.18, 108.85 ± 46.44 and 81.18 ± 18.05. This difference in mean values was significant with p-value of 0.000. There was significant difference in the different components of metabolic syndrome when compared among asthmatics with and without MS.

**Table 4. Comparison of Components of Metabolic Syndrome among Asthmatics with and without MS**

| Variables                  | Asthmatics with MS | Asthmatics without MS | p    |
|----------------------------|--------------------|-----------------------|------|
| Abdominal Girth            | 93.39±10.39        | 66.16±14.84           | 0.000|
| BP Systolic                | 132.39±8.24        | 119.89±8.78           | 0.000|
| BP Diastolic               | 85.00±5.9          | 75.76±5.66            | 0.000|
| Mean FBS (mg/dl)           | 118.16±28.64       | 82.48±9.81            | 0.000|
| Mean HLD (mg/dl)           | 36.34±5.85         | 49.52±8.18            | 0.000|
| Mean LDL (mg/dl)           | 105.16±28.36       | 81.18±18.05           | 0.000|

**Table 5. Comparison of Asthma Control Test in Asthmatics with and without MS**

| Asthma Control Test       | Asthmatics with MS | Asthmatics without MS | p value |
|---------------------------|--------------------|-----------------------|---------|
| Well Controlled           | 5.3%               | 67.7%                 | 0.000   |
| Partly Controlled         | 50.0%              | 27.4%                 | 0.000   |
| Uncontrolled              | 44.7%              | 8.9%                  | 0.000   |

**Table 6. Comparison of Asthma Severity in Asthmatics with and without MS**

| Asthma Severity       | Asthmatics with MS | Asthmatics without MS | p     |
|-----------------------|--------------------|-----------------------|-------|
| Intermittent          | 0%                 | 58.1%                 | 0.000 |
| Mild Persistent       | 36.8%              | 35.5%                 | 0.000 |
| Moderate Persistent   | 50.0%              | 6.5%                  | 0.000 |
| Severe Persistent     | 13.2%              | 0%                    | 0.000 |

**DISCUSSION**

The prevalence of metabolic syndrome is high among bronchial asthma patients which may be a reflection of the increasing prevalence of metabolic syndrome in the general population.20 The mean age of studied asthma patient was 37.41 ± 11.55 with age ranging between 18-65 years with 36% males and 64% females reflecting the high prevalence of asthma in females. Marco D R et al in 2000 reported mean age of asthma subjects was 33.8 ± 7.1 year and 52% were women,21 which shows similarity with our study. Kynk AJ et al reported asthma in young adults aged 15-34 years with a prevalence of 6.3% in men and 9.6% in women.22

In the present study of asthma patients, the metabolic syndrome was found in 38% of the asthma patients studied. In a study done in 2011, Uzunlulu M et al found the prevalence of metabolic syndrome in asthma patients was 36.7%,23 which is in concordance with our study. Another study done in 2010, Blanca E et al concluded that prevalence of metabolic syndrome was high (44.2%) among obese teenage asthmatics when compared with non-obese teenage asthmatics.24 A Nigerian study in 2012 found that the prevalence of metabolic syndrome was 17.7% among asthmatics.25

There was significant increase in the different components of metabolic syndrome in patients of asthma when compared with asthmatics without MS. Mean abdominal girth was 93.39cm in AS with MS and those without MS had mean of 66.16. This difference in the abdominal girth was significant with p-value 0.000. Mean fasting blood glucose was 118 mg/dl in AS with MS which was higher when compared with mean FBS of 82.48mg/dl in AS without MS, difference was significant (p-value 0.000). Mean systolic and diastolic blood pressure in AS with MS was higher as compared to AS without MS, 132.39 mmHg, 85.00 mmHg and 119.89 mmHg, 75.76 mmHg respectively, with significant p-value of 0.000. The mean HDL and Tg values were 36.34 and 163.11 respectively in asthmatics with MS while those without MS had values of 49.52 and 108.85. Those with metabolic syndrome had reduced HDL values with raised Tg levels, with significant difference (p-value 0.000).

Blanca et al studied that Obese male Asthmatics had significantly higher frequencies of metabolic abnormalities than Obese Non-Asthmatic males (higher BP, higher WC, and presence of ≥3 metabolic abnormalities).24 Brumpton B M et al in 2013 concluded that metabolic syndrome and two
of its components (high waist circumference and elevated glucose or diabetes) were associated with an increased risk of incident asthma in adults. The significant association was found between presence of metabolic syndrome and asthma severity and asthma control (p value <0.001). Almost half of the asthmatics with metabolic syndrome had partly controlled asthma with moderate persistent severity.

Olufunke O, A et al concluded similar results that those without metabolic syndrome had a better asthma control than those with metabolic syndrome. In a study from Spain, Sastre et al investigated the association between BMI and asthma control in a large sample of patients (607) with asthma. The percentage of patients with poor asthma control was slightly higher in participants with both low BMI (BMI < 18.5 kg/m²) and obesity (BMI > 30 kg/m²). In a smaller study by Kilic et al, the effect of obesity on asthma control was evaluated in 41 obese women with asthma and 40 non-obese women with asthma. The authors concluded that obesity is an important risk factor for uncontrolled asthma. Ko et al in 2009 found that the ACT correlates better with treatment decisions made by asthma specialists than spirometry, PEFR, or fractional exhaled nitric oxide measurements.

CONCLUSIONS

The prevalence of metabolic syndrome is high (38%) among the asthma patients. We also recorded poorer asthma control and more severe asthma in those with the metabolic syndrome. It is therefore necessary to screen patients with asthma for the components of metabolic syndrome and appropriate management may be indicated to improve overall outcome of asthma management.

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