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Effect of obesity and metabolic syndrome on severity, quality of life, sleep quality and inflammatory markers in patients of asthma in India

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Abstract

Introduction: The study aimed to compare the effect of obesity with and without metabolic syndrome on asthma severity, quality of life, sleep quality, sleep disordered breathing and inflammatory markers as compared to non-obese asthma patients.

Material and methods: 60 asthma patients recruited for the study were divided equally into non-obese (NOA), obese without metabolic syndrome (OANMS) and obese with metabolic syndrome (OAMS) groups. Study cohorts were assessed for severity of asthma, quality of life and quality of sleep using questionnaires and inflammatory markers (FENO, hs-CRP, IL-5, IL-6 and leptin). Institutional ethical committee approved the study.

Results: The results suggests OAMS patients may be a subtype of asthmatics having significantly severe asthma ($p < 0.05$), poor quality of life ($p < 0.05$), high risk of OSA ($p < 0.05$), decreased lung volumes (FRC) ($p < 0.05$), higher levels of inflammatory markers (leptin and IL-6) ($p < 0.05$), and high incidence of sleep disordered breathing ($p < 0.05$) in comparison to NOA and OANMS patients.

Conclusions: The present study has shown that obese asthmatics especially with metabolic syndrome represent a subtype of asthmatic population. Hence, the treatment of metabolic syndrome may be necessary in addition to asthma to achieve optimal control.

Key words: obesity, metabolic syndrome, asthma, SGRQ, FENO

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Introduction

Asthma and obesity represent growing epidemics both in the developing and in the developed world [1]. The parallel rise in the prevalence of asthma and obesity suggests that these disorders maybe linked. There is an increased prevalence of asthma in the obese and/or overweight subject; also obesity may be more prevalent in asthmatics than in non-asthmatics [2].

The obese-asthma phenotype is represented by a scarcity of airway inflammation. Obesity may predispose to increased Th2 inflammation or tendency to atopy, however other mechanisms independent of inflammatory infiltrates need to be studied, such as hyperglycemia, hyperinsulinemia and dyslipidemia in the context of metabolic syndrome. The metabolic syndrome is a cluster of risk factors that include hypertension, impaired glucose tolerance or diabetes mellitus, central obesity and dyslipidemia [3]. According to the HUNT study, metabolic syndrome is a risk factor for asthma [4].

Sleep disordered breathing (SDB), a condition frequent in obese individuals, may exacerbate asthma leading to its increased severity [5].

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Recently, changes in the expression of pro-inflammatory mediators such as leptin, IL-6, TNF-α, C-reactive protein and adiponectin have been demonstrated in obese asthmatics, implying their potential role in the pathogenesis of obesity--associated asthma [6]. Exhaled breath nitric oxide (FENO) levels are strongly and independently associated with respiratory impairment as well as bronchial hyper responsiveness [7].

The present study was consequently planned to compare the effect of obesity with and without metabolic syndrome on asthma severity, quality of life, sleep quality, SDB and inflammatory markers in comparison to non-obese asthma patients.

Material and methods

Patients diagnosed with asthma in line with the Global Initiative for Asthma (GINA) guidelines were enrolled for the study from the outpatient clinics [8]. A total of 60 asthma patients (32 females and 28 males) aged between 15 and 60 years were evaluated and were divided into 3 equal groups consisting of 20 patients each. The patients with BMI < 25 kg/m^2, were defined as non-obese and BMI ≥ 25 kg/m^2 were defined as overweight/obese [9]. The presence of metabolic syndrome was detected in line with the NCEP ATP III definition [10], if any 3 or more of the following were present 1) elevated waist circumference: men ≥ 90 cm, women ≥ 80 cm, 2) raised triglyceride (TG) > 150 mg/dL or on specific treatment for this lipid abnormality, 3) reduced HDL cholesterol < 40 mg/dL in males, < 50 mg/dL in females or on specific treatment for this lipid abnormality, 4) raised blood pressure: systolic > 130 mm Hg or diastolic > 85 mm Hg, or treatment of previously diagnosed hypertension, 5) raised fasting plasma glucose > 100 mg/dL or diagnosed type 2 diabetes. On evaluation of the above mentioned factors the patients were divided into 3 equal groups consisting of 20 patients each into: Group 1 — Non-obese asthmatics (NOA), Group 2 — Obese asthma without metabolic syndrome (OANMS) and Group 3 — Obese asthma with metabolic syndrome (OAMS). The exclusion criteria were 1) smoker (former and current smoker), 2) oral corticosteroid intake in the preceding month, 3) pregnant and lactating females, 4) patients with hepatic / neurologic disorder.

The severity of asthma was classified according to the criteria of the 2008 GINA classification as intermittent, mild persistent, moderate persistent and severe persistent [11]. SDB was defined as habitual loud snoring (partner/parent report of snoring "louder than talking" 3–4 times per week or more on a written questionnaire), and oxygen desaturation index (ODI) of 5 or more per hour during overnight oximetry monitoring [7].

Spirometry was performed on a dry, rolling-seal spirometer of the benchmark model lung function machine (P.K. Morgan, Kent, UK). Maximal expiratory flow volume curves were obtained as per ATS/ERS recommendations 2005 [12]. Three acceptable and at least 2 reproducible curves were obtained in each patient. The highest values of FVC and FEV_1 were selected. Spirometry was repeated 20 mins after inhalation of 200 μgm of salbutamol. Static lung volume like residual volume (RV) and total lung capacity (TLC) were measured. Helium was used to measure TLC [12].

St. George's Respiratory Questionnaire (SQRQ) measures health impairment in patients with asthma and COPD [13]. The questionnaire consist of 50 items that survey patient's recollection of their symptoms (symptom score), the disturbance to patient's daily physical activity (activity scores) and psychosocial dysfunction (impact scores).

Asthma Quality of Life Questionnaire (Junipers Asthma Questionnaire) is a 32-item questionnaire that measures the functional problems that are most troublesome to adults with asthma [14]. The items are in four domains (symptoms, activity limitations, environmental stimuli and emotional function).

Epworth Sleepiness Scale (ESS) evaluates general level of sleepiness. The patients were rated on 8 situations with a score of 0 to 30 (3 being the highest chance of dozing off) [15]. The maximum score is 24, and a score greater than 10 suggests the presence of excessive sleepiness.

Berlin questionnaire is a 10-item questionnaire that stratifies patients into a high or low risk category for sleep evaluation [16]. The Berlin questionnaire specifically evaluates snoring history and witnessed episodes of apnea (category 1; 5 questions), tiredness and sleepiness (category 2; 4 questions), and a history of high blood pressure and/or body mass index (BMI) > 30 kg/m^2 (category 3). Patients who scored positive in 2 of the 3 domains were considered high risk for OSA.

Pittsburgh Sleep Quality Index (PSQI) is a self-rated questionnaire, which assesses sleep quality and disturbances over a 1-month time interval. Nineteen individual items generate seven "component" scores subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [17].

The patients were kept overnight in the hospital for overnight pulse oximetry. Overnight pulse oximetry was performed with portable Smart link Oximeter that gives reading every 4-second. Patient's finger was placed inside the sensor for the entire sleep duration (minimal of 3 hours sleep). Recordings of SpO_2 were analyzed. Desaturation was considered if there is at least 4% fall in saturation from baseline. ODI was calculated as the total number of desaturations divided by the hours in bed (at least 3 hours of satisfactory reading) [7].

Serum TG level was estimated on fasting blood sample using standardized Beckman Coulter diagnostic kits on Beckman Coulter Synchron CX5 proclinical system. Serum HDL level was estimated on Trivitron Healthcare Nanolab — 240 clinical system.

High sensitivity C-reactive protein (hs-CRP), Il-5, Il-6, TNFα, values were measured with ELISA kits based on quantitative sandwich immunoassay as per manufacturer's instructions. Serum total IgE levels were estimated in all subjects by using MINILYSER-TECAN, Austria using Calbiotech kit using sandwich enzyme immunoassay technique. All subjects, regardless of their atopic status, underwent measurements of exhales nitric oxide using NIOX chemiluminescence analyzer (Aerocrine AB, Solna, Sweden) in accordance with the 2005 ATS/ERS recommendations [18].

All patients gave written informed consent to participate in the study. The institutional ethical committee approved the study protocol.

Statistical analysis

Using SPSS version 15.0 (SPSS, Chicago, IL, USA) software the data analysis was performed. The data was examined for distribution and homogeneity of variances was checked before applying parametric tests. The comparison of quantitative variables between three groups was done using ANOVA/Kruskal-Wallis test. The comparison of quantitative variables between two groups was done using unpaired t-test/Mann-Whitney test. The comparison of qualitative variables between two groups was done using Chi-square/Fisher's exact test. Statistical significance was used at the conventional 5% level ($p < 0.05$).

Results

60 patients with asthma, 28 males and 32 females, who were evaluated, ranged in age from 17 to 59 years, with duration of symptoms varying from 11 months to 31 years. The details of these patients are summarized in Table 1. The number of patients diagnosed with hypertension and/or are on anti-hypertensive drugs were maximum in the OAMS group (n = 10; 50%). Similarly, patients diagnosed to be diabetic and/or are on anti-diabetic drug were maximum in the OAMS group (n = 11; 55%). The family history of asthma was highest (70%) in the OANMS group.

The PFT parameters of the 3 groups have been described in Table 2. The significant pre-bronchodilator obstruction as denoted by pre-bronchodilator $FEV_1/FVC < 70\%$ and significant bronchodilator reversibility as denoted by change in FEV_1 or FVC 200 ml and > 12% change from baseline did not show any statistical difference between the three groups.

The questionnaires based assessment of the three groups has been described in Table 3. On evaluation of has the related quality of life in asthma, the SGRQ scores were worst in the OAMS

Table 1. General characteristics of study population (n = 60), by group[a]

Characteristic	NOA (n = 20)	OANMS (n = 20)	OAMS (n = 20)	p
Gender*				
Male	15 (75)	8 (40)	5 (75)	< 0.005
Female	5 (25)	12 (60)	15 (25)	< 0.005
Age, years**	30.10 ± 10.41	37.05 ± 11.23	40.90 ± 9.94	< 0.005
BMI, Kg/m^{2}**	22.08 ± 2.11	28.24 ± 2.22	30.42 ± 3.19	< 0.001
Duration of illness, years**	9.80 ± 8.98	13.15 ± 10.63	17.35 ± 13.63	0.106
Dyspnea, years **	9.80 ± 8.98	13.15 ± 10.63	17.35 ± 13.63	0.106
Cough, years **	9.80 ± 7.94	13.10 ± 11.15	15.90 ± 13.33	0.084

NOA — non-obese asthmatics; OANMS — obese asthmatics without metabolic syndrome; OAMS — obese asthmatics with metabolic syndrome, and BMI — body mass index. NOA group — BMI < 25 kg/m^2; OANMS group — BMI ≥ 25 kg/m^2 without metabolic syndrome; OAMS — BMI ≥ 25 kg/m^2 with metabolic syndrome; [a]values expressed as n (%) or mean ± SD; *Chi-square test; **One-way ANOVA and Tukey's post hoc test

Table 2. Pulmonary function test variables in (% of predicted) in the study population (n = 60)[a]

Variable	NOA (n = 20)	OANMS (n = 20)	OAMS (n = 20)
FVC	96.10 ± 10.80	91.85 ± 12.32	91.60 ± 7.65
FEV_1	86.85 ± 13.41	85.25 ± 14.64	84.00 ± 12.8
PEFR	56.75 ± 27.95	54.30 ± 25.61	65.95 ± 43.06
FEF25–75	87.35 ± 24.20	81.45 ± 28.18	94.25 ± 25.48
RV	107.60 ± 55.07	88.70 ± 18.81	98.61 ± 18.52
FRC	109.15 ± 28.21	93.80 ± 21.70*	85.44 ± 16.50**
RV/TLC	111.80 ± 39.56	107.50 ± 28.40	111.56 ± 16.52
TLC	97.30 ± 16.48	90.90 ± 12.26	91.89 ± 7.90
%DLCO	109.21 ± 19.96	101.95 ± 23.01	103.00 ± 23.89
DLCO/VA	124.68 ± 21.83	128.75 ± 26.49	132.94 ± 28.80

NOA — non-obese asthmatics; OANMS — obese asthmatics without metabolic syndrome; OAMS — obese asthmatics with metabolic syndrome, and BMI — body mass index. PEFR — peak expiratory flow rates; FEF 25–75% — forced expiratory flow; FRC — functional residual capacity; RV — residual volume; TLC — total lung capacity; DLCO — single breath diffusing capacity; DLCO/VA — single breath diffusing capacity corrected for alveolar volume. NOA group — BMI < 25 kg/m^2; OANMS group — BMI ≥ 25 kg/m^2 without metabolic syndrome; OAMS — BMI ≥ 25 kg/m^2 with metabolic syndrome; [a]values expressed as n (%) or mean ± SD; *p < 0.05 vs. NOA group; **p < 0.01 vs. NOA group; One-way ANOVA and Tukey's post hoc test

Table 3. Variables studying health related quality of life, risk of OSA, quality of sleep, severity of asthma, and SDB in the study population (n = 60)[a]

Variable	NOA (n = 20)	OANMS (n = 20)	OAMS (n = 20)
Health related quality of life in asthma			
a) SGRQ- Total score	27.18 ± 16.70	39.99 ± 12.12*	42.23 ± 4.35**
b) Juniper Questionnaire	4.55 ± 0.68	4.27 ± 0.51	4.21 ± 0.59
Risk of OSA			
a) Epworth Sleepiness Score (ESS > 10)	4 (20)	10 (50)^	11(55) ^ ^
b) Berlin questionnaire	3 (15)	7 (35)	10 (50)
Quality of sleep			
a) Pittsburg Sleep Quality Index (PSQI)	9 (45)	9 (45)	11 (55)
Severity of asthma			
a) intermittent	10 (50)	2 (10)	1 (5)
b) mild Persistent	8 (40)	10 (50)	9 (45)
c) moderate Persistent	2 (10)	8 (40)#	10 (50)##
d) severe Persistent	0	0	0
SDB	0	2 (10)	3 (15)%

NOA — non-obese asthmatics; OANMS — obese asthmatics without metabolic syndrome; OAMS — obese asthmatics with metabolic syndrome, and BMI — body mass index; OSA — obstructive sleep apnea; SDB — sleep disordered breathing; SGRQ — St. George respiratory questionnaire; NOA group — BMI < 25 kg/m^2; OANMS group — BMI ≥ 25 kg/m^2 without metabolic syndrome; OAMS — BMI ≥ 25 kg/m^2 with metabolic syndrome; [a]values expressed as n (%) or mean ± SD; *p < 0.01 vs. NOA group; **p < 0.01 vs. NOA group; ^p < 0.05 vs. NOA group; ^^p < 0.05 vs. NOA group; #p < 0.005 vs. NOA group; ##p < 0.005 vs. NOA group; % p < 0.05 vs. NOA group; One-way ANOVA and Tukey's post hoc test

group, followed by the OANMS and the NOA group, statistical significance of p < 0.003. However, the other Juniper questionnaire did not show any statistical difference between the groups. On assessment for risk of OSA, maximum number of patients with high-risk ESS score (ESS > 10) belongs to the OAMS group (p < 0.05). Similarly for Berlin questionnaire, the highest number was observed for the OAMS group, followed by the OANMS and the NOA groups, though the difference did not reach statistical significance. In PSQI questionnaire, the quality of sleep was the worst in the OAMS group, however, the result failed to reach statistical significance. Similarly, patients with sleep-disordered breathing were highest in the OAMS group, followed by the OANMS. None of patient in the NOA group had SDB. On assessment of severity of asthma at presentation, the NOA group had the highest (50%) of intermittent asthma, the OANMS had maximum

Table 4. Lipid profile and Inflammatory markers in the study population (n = 60)[a]

Variable	NOA (n = 20)	OANMS (n = 20)	OAMS (n = 20)
Lipid Profile			
Serum Triglyceride (mg/dL)	116.3 ± 93.3	138.9 ± 51.1	200.8 ± 95.7$^{*, **}$
HDL Cholesterol (mg/dL)	35.7 ± 16.1	39.1 ± 16.5	36.4 ± 14.1
Inflammatory markers			
FENO (ppb)	31.85 ± 11.82	25.15 ± 15.42	15.85 ± 10.04$^{\wedge, \wedge\wedge}$
S.Total IgE (IU/ml)	1363.83 ± 1193.48	1292.67 ± 1268.24	1578.74 ± 1099.44
AEC (cells/cumm)	366.00 ± 262.11	362.50 ± 216.34	328.00 ± 266.56
IL-5 (pg/ml)	36.85 ± 22.83	18.79 ± 11.74	33.60 ± 30.68
IL-6 (pg/ml)	41.95 ± 32.21	53.85 ± 40.88	118.99 ± 88.06$^{\#, \#\#}$
TNFα (units/ml)	194.55 ± 137.06	208.15 ± 143.57	267.00 ± 188.34
Leptin (ng/dL)	20.60 ± 14.37	39.70 ± 16.93$^{\%}$	37.75 ± 19.54$^{\%\%}$
Hs-CRP (mg/dL)	14.14 ± 6.72	14.20 ± 6.83	14.23 ± 6.98

NOA — non-obese asthmatics; OANMS — obese asthmatics without metabolic syndrome; OAMS — obese asthmatics with metabolic syndrome, and BMI — body mass index; OSA — obstructive sleep apnea; HDL — high density lipoproteins; FENO — exhaled nitric oxide; AEC — absolute eosinophil count; IL-interleukin; TNF — tumor necrosis factor; hs-CRP — highly sensitive C-reactive protein; NOA group — BMI < 25 kg/m^2; OANMS group — BMI ≥ 25 kg/m^2 without metabolic syndrome; OAMS — BMI ≥ 25 kg/m^2 with metabolic syndrome, [a]values expressed as n (%) or mean ± SD; $^{*}p < 0.01$ vs. NOA group $^{**}p < 0.01$ vs. OANMS group; $^{\wedge}p < 0.01$ vs. NOA group; $^{\wedge\wedge}p < 0.01$ vs. OANMS group; $^{\#}p < 0.01$ vs. NOA group; $^{\#\#}p < 0.01$ vs. OANMS group; $^{\%}p < 0.01$ vs. NOA group; $^{\%\%}p < 0.01$ vs. OANMS group; One-way ANOVA and Tukey's post hoc test

(50%) of mild persistent asthma patients. The results were statistically significant ($p < 0.005$); none of the groups had any patient diagnosed with severe persistent asthma.

The levels of lipid profile and inflammatory markers in the NOA, OANMS and OAMS have been depicted in Table 4. The mean serum triglyceride were highest in the OANMS group, the results being statistically significant ($p < 0.005$), however the mean HDL levels were the highest in the OANMS group, followed by the OAMS and the NOA groups, the difference was not statistically significant. Among inflammatory markers, mean FENO levels were the highest in the NOA group ($p < 0.001$) followed by the OANMS and the OAMS group. Subsequently, it was noted that IL-6 levels were highest in the OAMS group ($p < 0.003$), followed by the OANMS and the NOA group. The mean serum leptin levels were the highest in OANMS group ($p < 001$).

Discussion

The primary objective of the study was to compare the NOA, OANMS and OAMS group patients with respect to asthma severity, quality of life, quality of sleep, OSA, inflammatory markers and sleep disordered breathing

The effect of obesity and metabolic syndrome on the severity of asthma at presentation is not well established. A retrospective cohort analysis of National Health and Nutrition Examination survey 2001−2002 and 2002−2004 reported 2.63 fold-increased odds of moderate to severe asthma in centrally obese patients [19]. The current study had increased number of moderate persistent asthmatics in obese groups while non-obese asthmatics mainly suffered from mild intermittent and mild persistent asthma. Lazarus et al. have described in obesity a disproportionate reduction in FVC in comparison to FEV_1 [20]. In the current study, no statistically significant reduction in FVC and FEV_1 with increasing BMI was observed. However, mean percent predicted FRC in current study was the highest in NOA, decreasing in OANMS and further decreasing in OAMS groups ($p < 0.005$). These results are consistent with the literature [21]. Also the largest reduction in FEV_1 and FVC in OAMS group might be attributed to additional effects of metabolic syndrome on obese asthmatics.

Nakajima et al. concluded that impaired restrictive pulmonary function, but not obstructive pattern, might be associated with metabolic disorders and metabolic syndrome in a severity dependent manner [22]. This may give a possible explanation of significantly reduced lung volume in OAMS group. The plausible explanation for this is increase in intra-abdominal pressure on the diaphragm and in fat mass on the chest wall leading to mass loading of the thorax, thus increasing the deflationary pressure and reducing the compliance of lung and the respiratory system [23].

A prior study on 200 adult asthmatics by Malej et al. in Tunisia assessed quality of life by the

AQVAT (Arabic version of the Asthma Quality of Life Questionnaire) [24]. The univariate analysis showed that obesity and overweight were associated with a poorer quality of life (AQVAT > 6). Ermolova et al. reported in their assessment of the quality of life based on the short ShortForm-36 questionnaire, a marked negative effect of asthma with metabolic syndrome patients in comparison to asthma without metabolic syndrome [25]. In the current study, similar poorer quality of life as assessed by the SGRQ score was the worst in OAMS group.

Sleep apnea is considered as a manifestation of metabolic syndrome, as there is a strong association of OSA with obesity, systemic effect e.g. hypertension and diabetes, overlapping with the factors associated with the metabolic syndrome [26]. The current study reported OAMS (55%) or OANMS (50%) groups were having higher risk of OSA as compared to NOA (20%), as assessed by ESS score. Similarly, using Berlin questionnaire a statistically significant difference could be found between NOA and OAMS groups. The potential mechanism for increased risk of OSA in asthmatics has been attributed to presence of persistent airway mucosal inflammation in asthma, which may promote a reduction in the surface area of the airways, including the upper airway. The reduction in surface area of pharynx provides a prime setting for the development of OSA [27].

The data regarding FENO levels in obese asthmatics is conflicting; Ramasamy et al. found no difference in FENO levels related to obesity [23], whereas Komakula et al. observed the trend towards increased FENO in obese adults with severe asthma [28]. The current study demonstrated significantly lower levels of FENO in OAMS in comparison to NOA and OANMS groups. These results are in line with a population-based study by Berg et al. in obese asthmatics that have shown negative correlation between BMI and FENO [26]. In our study the levels of IL-6 were significantly higher in OAMS group. The further increased levels found in metabolic syndrome are in line with a study by Kern et al. who have demonstrated the strongest relationship of IL-6 with obesity and insulin resistance [29]. The leptin levels in the present study were higher in obese asthmatics in comparison to non-obese, however presence of metabolic syndrome did not showed significant difference among obese asthmatics. The findings of present study are in agreement with the literature [30]. However, other inflammatory markers (IL-5, TNFα and hs-CRP) failed to demonstrate any statistical difference among the groups. Positive association of TNFα and hs-CRP levels with obesity has been documented in the literature [6]. The present study is limited by small number of patients enrolled. Hence, a large scale population based study in future may be planned for assessing the effect of obesity and metabolic syndrome on asthma in Indian population.

In conclusion, present study has shown that obese asthmatics especially those with comorbidities like metabolic syndrome may be considered as a subtype of asthmatics having more severe asthma, poor quality of life, high risk of OSA, decreased lung volume (FRC), higher levels of inflammatory markers like leptin and IL-6 and high incidence of SDB. The obesity asthma group has been recently recognized as a new subphenotype in the GINA classification. Obesity may represent a contributory factor in poor control of asthma with standard asthma therapies. One of the unmet needs in asthma treatment is to develop personalized therapies targeted towards a specific phenotype. Large cohort studies with a longitudinal follow up are required to better define the subgroups within the obesity asthma phenotype.

Conflict of interest

The authors declare no conflict of interest.

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