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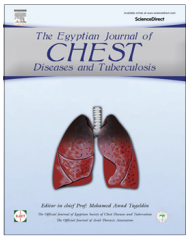

ORIGINAL ARTICLE

Effect of weight reduction on obese patients with COPD and bronchial asthma

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KEYWORDS

Asthma;
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Abstract There is a link between obesity and both, asthma and COPD.

Aim of the work: To study effect of weight reduction on pulmonary function tests of obese COPD and bronchial asthma patients.

Subjects and methods: 2 groups were included, group(G)I, 30 obese COPD and GII 30 obese bronchial asthma patients. Pulmonary function tests were done to all participants before and after weight reduction.

Results: GI showed increased FRC, ERV and RV significantly, IC was significantly decreased and GII showed increased FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25-75\%}$ and ERV significantly after weight reduction.

Conclusion: Weight reduction improved airway obstruction, increased ERV, RV, FRC and DLCO either significant or insignificant in asthma and COPD.

Introduction

Obesity has recently been identified as a major risk factor for the development of asthma. Asthma tends to be more severe in obese individuals, and it does not respond adequately to treatment. As a result, the combination of obesity and asthma is becoming a major public health issue in many countries [1]. Chronic inflammation is thought to initiate and perpetuate cycles of tissue injury and repair in asthma. The persistence of inflammatory cells within the airways and the up-regulation of a number of inflammatory cytokines and growth factors such as tumor necrosis factor (TNF), tumor growth factor beta (TGF-b) and several members of the interleukin family, as well as adhesion molecules, participate in the onset of lung remodeling [2,3]. Yeh and Huang showed that, in the murine model, increase in dietary cholesterol resulted in enhanced pulmonary allergic inflammation [4]. It was traditionally thought that COPD patients were less likely to be obese. The rationale was that systemic inflammation, in the more advanced stages of disease, would lead to cachexia [5] rather than overweight. However, in the most recent studies, looking at the association of high BMI and COPD, approximately two thirds are overweight or obese [6]. A BMI below 21 kg/m^2 was shown to be a negative prognosis marker [7] while obesity appears to convey a survival advantage in COPD, as it is the case in other chronic disease [8].

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However, data relating to this so called "obesity paradox", whereby obesity seems beneficial on survival, are often biased. Clinical experience indicates that the combined restrictive/obstructive deficits evident in obese patients with COPD culminate in worsening symptomatology and activity limitation [9].

Aim of the work

The aim of the work is to study the effect of weight reduction on pulmonary function tests of obese COPD and bronchial asthma patients.

Subjects and methods

This study was conducted on 60 patients, in Chest Department – Tanta university hospitals from January 2014 to April 2015, and divided into 2 groups, group(G)I, included 30 obese non-smoker COPD patients, their mean age was 47.2 ± 1.3 years (17 males and 13 females) GII included 30 obese, non-smoker bronchial asthma patients, their mean age was 45.6 ± 2.6 years (15 males and 15 females). All persons were subjected to the following:

(1) Full history taking and clinical examination including body mass index (BMI).
(2) Plain X-ray chest P.A view.
(3) ECG and Echocardiography.
(4) Complete pulmonary function tests including spirometric study, lung volumes and diffusion. These were carried out by Care Fusion Germany 234 Gmbh, Version 03.00, V-781267-057, For JLAB software ⩾5.70, Disposable and accessories (Leibniz strasse 7-97204, Hoechberg, Germany, email: MarketingInfo.EU@carefusion.com).

Spirometric study: including

Slow spirometry

The patient is asked to close his nose with the nose-clip and approach the mouthpiece. He should breathe quite normally. Tidal breathing was displayed on the screen. After about 8 breaths, the following was done:

(1) From normal breathing, the patient should slowly breathe out to a maximum, slowly breathe into a maximum and then slowly breathe out to a maximum.
(2) Then he should continue to breathe quite normally.

Forced spirometry

(1) From normal breathing, the patient should slowly breathe out to a maximum, slowly breathe into a maximum, breathe out as deeply and much as possible and then breathe in as deeply and completely as possible.
(2) Then he should continue to breathe quite normally. From this spirometric study, the following were measured: FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25–75\%}$, expiratory reserve volume (ERV) and estimated inspiratory capacity (IC).

Functional residual capacity (FRC)-helium (He) rebreathing

A disinfected mouthpiece was attached to the disinfected pneumotach, O_2 gas cylinder was opened and rebreathing bag (RB) was connected. With starting the measurement program, the rebreathing bag was emptied, flushed with O_2 and a zero adjustment of the He gas analyzer was performed. Then the RB bag was filled with helium and oxygen according to the preset filling volume and its contents were analyzed. The patient was asked to approach the mouthpiece and close his nose with the noseclip. He should breathe quite normally. From normal breathing, the patient was asked to slowly breathe out as deeply as possible and then continue to breathe normally. The patient breathed the gas mixture consisting of about 9% helium and 32% oxygen contained in the RB bag. In order to keep the oxygen content in the RB constant, about 250–300 ml oxygen per minute was added. The inhaled He gas mixture was spread out evenly into the lung. The trend of the He wash-in curve should be observed and the He value was displayed in the status line. The following were measured: total lung capacity (TLC), residual volume (RV) and FRC.

Diffusion-single breath (SB) study

SB gas cylinder was opened and after an automatic zero adjustment, the actual measurement was started. The patient should be asked to approach the mouthpiece and to close his nose with the nose-clip. He should breathe quite normally. After at least three breaths, the patient was asked to exhale as deeply as possible from normal breathing. After maximal expiration the patient was requested to inhale fast as deeply as possible, then the patient inhaled the gas. The occlusion time automatically started after 1/3 of inspiration. At the end of inspiration, the patient was prevented from expiration for the period of time set as occlusion time. The patient had to keep the mouthpiece in his mouth and hold his breath for 10 s. The pressure curve displayed during the occlusion showed whether the patient had held his breath or whether he had tried to expire or inspire despite the occlusion. After the set occlusion time had expired, the shutter was opened and the patient was required to exhale smoothly, without hesitation or interruption and sampling volume was exhaled via the sampling tube. The gas sample collected for analysis remains in the tube. The remaining air was exhaled via the opened shutter. The sampling valve was closed and the patient could leave the mouthpiece and thus diffusing Capacity of carbon monoxide (DLCOSB) was measured. Informed consent was taken from all participants. All patients shared in weight reduction program achieved by using low caloric diet (500–1000 calories less than recommended daily allowance, which calculated according to The Harris–Benedict equations) for 6 months [10]. 14 (9 from group I and 5 from group II) patients could not continue the weight reduction program and were excluded from the study, then after weight reduction, pulmonary function tests were repeated to all participants.

Including criteria:

(a) Obesity must be $\geqslant 30\ kg/m^2$.
(b) Diagnosis of asthma was considered if [11]:
  - There were symptoms of dyspnea, cough and/or wheezing, especially nocturnal with acute episodes which were characterized by hyperinflation of the thorax, decreased breath sounds and high pitched wheezing.
  - Symptoms were worse in the presence of exercise, viral infections, inhaled allergens, irritants, changes in weather, strong emotional expression, stress, menstrual cycles.
  - Reversible airflow obstruction: increase in FEV_1 $>12\%$ of predicted after inhalation of bronchodilator.
  - Alternative diagnoses were excluded.

c-COPD could be diagnosed if [12]: there were chronic chest symptoms especially cough, shortness of breath and sputum production. FEV_1/FVC ratio was $<70\%$ and percent of recovery after single dose of bronchodilator was $<15\%$.

All patients shouldn't have cardiac troubles, DM or other chest diseases rather than asthma and COPD.

Results

In the obese COPD group, there was an insignificant increase of percent of predicted of FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25-75\%}$, DLCO and TLC after weight reduction. Percent of predicted of FRC, ERV and RV were significantly increased after weight reduction. In contrast, percent of predicted of IC was significantly decreased (Table 1). In the asthma group, percent of predicted of FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25-75\%}$ and ERV were significantly increased after weight reduction but percent of DLCO, TLC, RV and FRC were insignificantly increased, but, percent of predicted of IC was insignificantly decreased (Table 2).

Discussion

Guimaraesa et al. found that FEV_1 and FVC were normal in obese persons but they were significantly increased after weight reduction [13]. Lazarus et al. found that the FEV_1 to FVC ratio decreases with increasing BMI in overweight and obese individuals [14]. In morbidly obese subjects, Biring et al. found a reduction in mid-expiratory flows and the FEV_1 to FVC ratio [15]. Sahebjami and Gartside found that reduced FEV_1 and FVC in obese subjects were associated with normal

Table 1 Spirometric, lung volumes and diffusion studies in obese COPD patients before and after weight reduction (W.R).

	G I (Before W.R)		G I (After W.R)		*t* Test	*p* Value
	Range	Mean S. D	Range	Mean S. D		
FEV_1	44–52	47.6 ± 3.21	49–55	51.2 ± 2.68	3.703	0.091
FVC	70–87	77.2 ± 6.53	74–89	83.4 ± 7.30	2.002	0.195
FEV_1/FVC	45–52	48.2 ± 3.11	44–55	50.8 ± 4.76	1.043	0.337
PEFR	54–62	58.6 ± 2.88	56–64	60.8 ± 3.27	1.274	0.292
$FEF_{25-75\%}$	28–35	32.8 ± 2.95	27–40	34.8 ± 5.89	0.461	0.516
DLCO	64–82	72.2 ± 6.50	71–85	77.2 ± 5.07	1.841	0.212
TLC	100–121	112.8 ± 8.47	110–135	123.4 ± 11.35	2.802	0.133
FRC	131–146	138.2 ± 7.05	155–175	165.2 ± 7.92	32.429	0.001*
RV	150–178	163.6 ± 11.28	180–199	191.8 ± 7.89	20.983	0.002*
ERV	64–91	75.8 ± 9.71	101–120	111 ± 7.97	39.285	0.001*
IC	80–87	83.4 ± 2.70	70–78	74 ± 3.54	22.313	0.001*
BMI	32–38	34.6 ± 2.19	26–29	27.4 ± 1.52	36.507	0.001*

* Significant.

Table 2 Spirometric, lung volumes and diffusion studies in obese asthmatic patients before and after weight reduction (W.R).

	G II (Before W.R)		G II (After W.R)		*t* test	*p* Value
	Range	Mean S. D	Range	Mean S. D		
FEV_1	66–75	69 ± 5.74	83–87	84.75 ± 1.71	5.036	0.049*
FVC	72–82	78 ± 4.64	90–95	93 ± 2.94	3.472	0.048*
FEV_1/FVC	84–95	89 ± 4.00	88–94	91.25 ± 5.12	1.968	0.203
PEFR	40–54	47 ± 5.57	56–67	62 ± 4.97	17.677	0.004*
$FEF_{25-75\%}$	39–54	45.6 ± 5.41	50–59	54.5 ± 3.70	7.789	0.027*
DLCO	95–111	103 ± 5.66	100–112	105.25 ± 5.12	0.381	0.557
TLC	82–94	86.8 ± 5.22	82–96	88 ± 5.83	0.106	0.754
FRC	75–92	84 ± 6.60	85–97	91.25 ± 5.06	3.261	0.114
RV	100–125	113.4 ± 9.40	105–121	114.75 ± 7.41	0.055	0.822
ERV	60–78	71 ± 7.00	81–90	85.25 ± 3.69	13.342	0.008*
IC	71–80	74.8 ± 3.35	66–75	70.25 ± 3.69	3.764	0.094
BMI	32–40	36.6 ± 2.97	27–30	28.5 ± 1.29	25.388	0.001*

* Significant.

FEV_1 to FVC ratio [16]. Li et al. found reduced FRC and diffusion impairment and this, reduction in static lung volume was correlated with the degree of obesity [17]. Obese subjects had a reduction in the expiratory reserve volume (ERV) due to decreased FRC by the mass loading effect of obesity. This may be accompanied by regional gas trapping in poorly ventilated lung units due to small airway closure and subsequent atelectasis [18]. Biring et al., Jenkins and Moxham concluded that TLC was normal in both mild and morbid obesity [18,19]. Guimaraesa et al. found that TLC was normal in obese persons and was significantly increased after weight reduction [13]. In contrast, FRC and RV were less than normal levels and after weight reduction, there was a significant increase of FRC but insignificant as regards RV [13]. Carbon monoxide diffusion capacity (DLCO) increased with increasing obesity and reversed with weight loss due to an increase in pulmonary blood volume. Also, DLCO is directly related to the lung volume at which it is measured and any tendency toward reduced lung volumes with obesity will decrease DLCO. A low to normal DLCO in obesity may represent a loss of pulmonary capillary bed (as seen with atelectasis), especially at high BMIs [20]. In this study, obese COPD patients showed an insignificant increase of percent of predicted of FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25–75\%}$, DLCO after weight reduction, but percent of predicted of FRC, ERV and RV were significantly increased after weight reduction. In contrast, percent of predicted of IC was significantly decreased. Ora et al. explore the relationship between obesity and operating lung volumes in patients with moderate to severe COPD. Contrary to current beliefs, the combination of obesity and COPD was not associated with diminished exercise capacity or greater dyspnea compared with normal weight patients with similar reduction in FEV_1. They found also, relatively reduced lung hyperinflation in obese patients with COPD due to reduced operating lung volumes at rest [21]. In the general population, obesity is an established risk factor for reduced life expectancy, independent of smoking status [22]. Paradoxically, epidemiological studies have shown that the patients with advanced COPD who are overweight or mildly to- moderately obese have a survival advantage compared with underweight patients [23]. This ''obesity paradox'' has also been described in other chronic diseases (chronic heart failure, rheumatoid arthritis, and chronic renal disease) but the protective mechanisms are unknown [24]. It is noteworthy that this reduced risk of mortality was not observed in obese patients with milder COPD [25] and that subgroups of COPD patients with more severe obesity are at a greater risk of death due to respiratory failure than normal weight COPD [26]. There is an exponential relation between increasing BMI and decreasing ERV [27]. This volume reduction effect occurs across all severity stages of airway obstruction and is seen even as BMI increases from normal weight to the overweight range. TLC and RV are relatively less affected by the increasing weight in COPD. Importantly, as in health, the resting IC increases in response to increasing BMI across all severity stages, reflecting the greater reduction in end expiratory lung volume relative to TLC [28]. Obesity and COPD have various influences on respiratory physiology, some are similar and some are opposite. The relationship between BMI and either functional residual capacity or expiratory reserve volume is not affected by the presence of airflow obstruction [21]. However, obese COPD patients are less hyperinflated compared to their lean counterparts [21]. Moreover, for a given FEV_1, IC is higher in obese subjects [29]. These changes seem beneficial to COPD subjects, counteracting some of the deleterious effects of the disease. However, oxygen consumption is higher for a given workload for obese subjects, leading to higher ventilatory demand. This increased ventilatory requirement further stresses the respiratory system whose capacity is already reduced by the presence of airflow limitation [30]. Adipose tissue is the main lipid storage depot in the body and is of crucial importance in buffering the daily influx of dietary fat entering the circulation. One characteristic of adipose tissue in obesity is the enlargement of adipocytes which may represent impaired adipocyte differentiation. The hypertrophic adipocytes of obese subjects are overloaded with stored triacylglycerol and it is likely that the buffering capacity for further lipid storage in these adipocytes is decreased, especially in the postprandial state. Non-adipose tissues are therefore exposed to an excessive influx of lipids which could lead to ectopic fat deposition [31]. Adipose tissue is often considered to be an abundant source of pro-inflammatory mediators [32]. Systemic inflammation is considered a hallmark of COPD [33] and increased levels of pro-inflammatory mediators have been reported in the circulation of COPD patients [30]. However, not all patients with COPD demonstrate systemic inflammation. In the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study, only 16% of patients with COPD had persistent systemic inflammation at baseline [34]. However, it is interesting to note that the patients with systemic inflammation in this study were more obese, with a mean BMI of 29.4 Kg/m^2, compared to a mean BMI of 25.6 Kg/m^2 in the group without persistent systemic inflammation [34]. Increased levels of systemic inflammation had been earlier reported in relation to excessive fat mass in COPD patients. Specifically, tumor necrosis factor-α, interleukin (IL)-6 and leptin levels in plasma have been shown to be significantly increased in overweight/obese COPD patients compared with normal-weight patients [35] and the likelihood of having elevated C-reactive protein in COPD patients was found to be 3.3 times higher in obese patients compared to normal-weight patients, after adjusting for relevant confounders [36]. A study by Rutten et al. also demonstrated that abdominal fat mass is positively associated with plasma C-reactive protein levels in patients with COPD [37]. Interestingly, it has been shown that non-obese patients with COPD with more visceral fat mass compared to control subjects were associated with increased IL-6 levels [38]. McDonald et al. concluded that, in obese COPD patients, dietary energy restriction coupled with resistance strength training results in clinically significant improvements in BMI, exercise tolerance and health status, while preserving skeletal muscle mass and importantly, this intervention resulted in an improved prognostic score [39]. In the present study, obese asthmatic patients showed that percent of predicted of FEV_1, FVC, FEV_1/FVC, PEFR, $FEF_{25–75\%}$ and ERV were significantly increased after weight reduction but percent of DLCO was insignificantly increased. Hakala et al. concluded that weight loss reduces airway obstruction as well as peak expiratory rate variability in obese patients with asthma [40]. As patients decreased their body mass index from 37.2 Kg/m^2 to 32.1 kg/m^2, diurnal PEF variation declined from 5.5% to 4.5%,day-to-day variation declined from 5.3% to 3.1%. The mean morning PEF, $FEF_{25–75\%}$, FEV_1, FVC, FRC and

ERV increased after weight loss [40]. Camargo et al. carried out one of the first longitudinal studies in adults, showing that women who gained weight after 18 years of age ran a greater risk of developing asthma in the next 4 years, regardless of caloric intake or physical activity [41]. Castro-Rodríguez et al. in the first longitudinal study of a pediatric population, showed that girls, but not boys, who became obese or overweight between 6 and 11 years of age ran a 7-fold greater risk of developing asthma than those who maintained normal nutrition and growth [42]. Stenius-Aarniala et al. and Dhabuwala et al. concluded that when obesity precedes the onset of asthma, it has a greater effect on progress of disease and weight reduction either by diet or gastric bypass has been reported to improve asthmatic symptoms [43,44]. Obesity produces decreased tidal volume and functional residual capacity, both of which reduce the tidal stretch of smooth muscle thus, the ability to respond to natural stress such as exercise is hampered by small tidal volumes [45]. Also, Obesity increased gastro-esophageal reflux due to accompanied esophageal sphincter relaxation, resulting in esophageal acid reflux passing into the trachea and airways. The direct contact of gastric acid with the airways causes bronchoconstriction owing to the resulting micro-aspiration or to the vagal reflex [46]. Leptin plasma levels have been positively correlated with body fat, stimulating the release of tumor necrosis factor (TNF-α) by adipocytes and act on the sympathetic nervous system which is crucial in controlling airway tone and diameter; important factors in asthma [47]. TNF-α is elevated in asthma and is related to the production of T helper-2 cytokines as IL-4 [48]. There are common genes, playing a role in both asthma and obesity as chromosomes 5q, 6, 11q13, and 12q [45]. Adipose tissue contains the enzyme aromatase, which is responsible for converting androgens into estrogens causing airway hyper-reactivity and greater severity of irreversible airflow obstruction [49]. Saraivaa et al. found that experimentally induced obesity in mice leading to alveolar collapse, bronchoconstriction, increased collagen fiber content in airways and alveolar septa also, the high fat diet led to a further increase in epithelial cell detachment, eosinophil and neutrophil infiltration, and elastic fiber fragmentation [50]. Obesity yielded larger chest wall circumferences, which resulted in lower tidal volume, alveolar collapse, and a reduction in the diameter of airways. However, in the presence of obesity, asthma is not simply a mechanical phenomenon. In this line, Shore and colleagues have shown that obese mice have increased airway hyper-responsiveness independent of lung volume [51], possibly associated with augmentation of the inflammatory process. The impact of obesity on the remodeling process may result from chronic repetitive injury to the airway wall caused by inflammation [52]. Increased IL-4 and IL-5 may play a role in the regulation of collagen synthesis by stimulating transforming growth factors (TGF) and increasing the expression of type I collagen through activation of transcription factors [53]. Furthermore, VEGF may also cause a marked increase in inflammation, followed by infiltration with mononuclear cells, eosinophils, and neutrophils in lung parenchyma [54], also, Lumeng et al. and Foster et al. concluded that obesity is accompanied with pulmonary inflammation and remodeling due to lipid droplet accumulation in lungs through pulmonary lipotoxicity [55,56]. Ghobashy et al. found that collagen deposition and elastic fiber destruction could be reversed when inflammatory process improved due to removal of the triggering cause, such as air pollution in their study [57] and this might occur in this study due to weight reduction and thus, explained the improvement of airway obstruction. So, it was concluded that weight reduction improved airway obstruction insignificantly in obese COPD and significantly in asthma and increased ERV, RV and FRC. As regards DLCO, it was increased in both COPD, asthma after weight reduction. Some demerits are present in this study, control and obese groups are preferred to be included, also, study of some mediators in blood and bronchoalveolar lavage and measurement of waist circumference and visceral fat in addition to BMI may be helpful.

Conflict of interest

No conflict of interest.

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