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Review Article

Obesity and Asthma: Physiological Perspective

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Obesity induces some pertinent physiological changes which are conducive to either development of asthma or cause of poorly controlled asthma state. Obesity related mechanical stress forces induced by abdominal and thoracic fat generate stiffening of the lungs and diaphragmatic movements to result in reduction of resting lung volumes such as functional residual capacity (FRC). Reduced FRC is primarily an outcome of decreased expiratory reserve volume, which pushes the tidal breathing more towards smaller high resistance airways, and consequentially results in expiratory flow limitation during normal breathing in obesity. Reduced FRC also induces plastic alteration in the small collapsible airways, which may generate smooth muscle contraction resulting in increased small airway resistance, which, however, is not picked up by spirometric lung volumes. There is also a possibility that chronically reduced FRC may generate permanent adaptation in the very small airways; therefore, the airway calibres may not change despite weight reduction. Obesity may also induce bronchodilator reversibility and diurnal lung functional variability. Obesity is also associated with airway hyperresponsiveness; however, the mechanism of this is not clear. Thus, obesity has effects on lung function that can generate respiratory distress similar to asthma and may also exaggerate the effects of preexisting asthma.

1. Introduction

The obesity prevalence has alarmingly and unprecedentedly increased by more than 3-fold in last three decades, irrespective of socioeconomic status, gender, or age, worldwide [1]. Globally, there are more than 1 billion overweight adults which constitute 300 million clinically obese individuals [1].

Obesity is the prime risk factor for various morbidities related to cardiovascular system, metabolic system, and endocrine system. However, in the last 50 years there is a consistent accumulation of evidence to suggest that obesity can significantly impair respiratory well being as well. There is substantial evidence to suggest that obesity enhances the risk of having asthma [2–30] antedate development of asthma [3, 4, 6, 20] and induces asthma worsening amongst preexisting asthmatics [30–33]. The mechanism of this link is however not fully understood and elucidated.

The current mechanistic understanding of asthma and obesity is a complexity of dietetic factors deficient in antioxidants [34–39], attributes of reduced physical exercise [40, 41], gastroesophageal reflux disease (GERD) [42–44], components of systemic inflammation released from adipose tissue, and mechanical restriction imparted on lung excursions by thoracoabdominal fat [6–8]. Nevertheless, there is a general consensus that obesity increases the metabolic oxygen demand and alongside impairs the lung-diaphragmatic movement. This induces enhanced workload on the lung mechanics to comply with bodily oxygen needs. Hence, obesity is an intriguing clinical state of virtual respiratory distress without respiratory illness.

In this review we will primarily discuss the physiological changes in the lungs caused by obesity, with its potential role in inducing lung physiology conducive to asthma clinical state.

2. Obesity and Asthma Epidemiological Perspective

Obesity has been linked to asthma in various cross-sectional and prospective studies with odds ratio of 1.5–3.5 and relative risk of 1.1–3.5 across adult and paediatric populations [3, 8]. Further, some studies have failed to demonstrate any direct obesity-asthma associations, however, having elucidated positive relation between adipokines (adiposity related

inflammatory mediators) and asthma in same populations [45] which indirectly links obesity to asthma. The obesity asthma link is largely attributed to female gender [8, 12–15, 17, 46–48]. However, there is enough evidence to suggest that obesity enhances the risk of asthma in male populations as well [10, 11, 16, 20]. Weight has also demonstrated a dose response association with asthma symptoms [2, 3, 5–8]. In a retrospective study of 143 adults, Akerman et al. [49] demonstrated linear relationship ($r = 0.40$, $P = 0.0001$) between asthma severity and body mass index (BMI). In another study, Varraso et al. [50] had shown that with each $1\,kg/m^2$ the asthma severity score changes by 0.183.

Despite the strong link between asthma and adiposity there are few studies which have failed in elucidating any link between asthma and obesity. This is particularly observed in males and paediatric population [19, 51–56]. Asthma-obesity studies have some pertinent methodological limitations, particularly over reliance on self-reporting of symptoms age and height, and inadequate sample size issues, which could have contributed to the absent obesity-asthma link in some studies. However, it is also important to mention that asthma and BMI demonstrate a U shaped relation [7, 8]. Both extreme high and low BMIs enhance risk of developing asthma [7, 8]. Largely many obesity and asthma studies have compared overweight and obese BMI individuals versus nonobese BMI subjects as control populations. This generates a pertinent risk of also including low BMI high asthma risk population in nonobese BMI comparative groups, which could have negated obesity-asthma associations in some studies.

Additionally, BMI has potential to overdiagnose obesity. BMI defines size of body structure rather than true obesity, which constitutes fatty mass plus body masculinity. The adiposity impacts negatively on the lung functions, while the masculinity impacts positively on the lung functions [57–66]. Physiologically, males have more muscle mass than females. Further, BMI in children may not adequately distinguish increased lean tissue mass from increased fat mass. Therefore, BMI is not always an appropriate marker to study obesity associated diseases in male gender and paediatric populations. This however ensues requirement of actual measure of body adiposity, such as waist/hip ratio (WHR), which reflects central adiposity, subscapular skin-fold thickness, which reflects thoracic adiposity, and skin-fold thickness which reflects general obesity.

Obesity induced lung restriction is one of the prime factors contributing to deranged respiratory mechanics. Therefore, the potential role of body fat distribution in induction of asthma obesity relationship cannot be neglected. It is the abdominal and thoracic fat which interdependently imparts mechanical restriction to the excursions of diaphragm and lungs. The fatty tissue deposits on other bodily sites such as the hips and thighs will not affect the lung movements. In a recent study, Park et al. had shown that overall body fat perse does not contribute to low lung volumes in males, while abdominal obesity significantly reduced FEV1 and FVC irrespective of gender [67]. It is believed that there is more thoracoabdominal fat deposition in females compared to males. This could also be a reason for small airway calibre in females and relatively more obesity predisposition towards asthma in females compared to males.

Further it has been shown that asthma is more common amongst obese girls who have achieved puberty and menarche earlier. There is also an evidence to suggest that postmenopausal usage of estrogens enhances risk of asthma [25, 50]. Also, progesterone which is known to induce smooth muscle relaxation is decreased in obese states [68, 69]. Such observations cue towards probable role of estrogens-progesterone modulation in obesity in development of asthma in women during puberty. In addition, in a study, Gold et al. followed a group of 9,828 children aged 6–14 years over median period of five years in six US cities to evaluate asthma incidence in the paediatric population [22]. Age of 6–14 years also implies peak period of lung growth. This study showed that during the entry into the study there was an increased risk of a new asthma diagnosis amongst girls with higher BMI, which was not demonstrated in boys. However, there was an increased risk of asthma amongst both boys and girls with largest annual increase in BMI during follow-up period [22]. This study implies that obesity effects during sensitive period of peak lung growth in human life could enhance risk of asthma in future. Also, in women, the age of peak lung growth occurs earlier. Hence, the current presence of obesity may not be enough history to demonstrate associations with asthma. It is important to probe historical trends of obesity, particularly obesity in childhood and adolescence, while probing obesity-asthma associations. This has been largely neglected in most studies. Presence of childhood obesity with current nonobese status could have also contributed to lack of obesity-asthma link.

3. Obesity and Physiological Airway Obstruction

High BMI in adults has been associated with reduced FEV1 and FVC [70–72]; however, the FEV1/FVC ratios are minimally reduced due to equivalent decrease in FEV1 and FVC [73, 74]. On the other hand, in children, except for moribund obesity state, increasing BMI has been associated with increasing FEV1 and FVC, however, with reduction in FEV1/FVC ratio [75, 76]. Nevertheless, results of correlation between spirometric lung volumes and body composition have been diverse in each study. These associational variations resulted in a general consensus, that effect of adiposity on lung volume is modest, and both FEV1 and FVC are usually within the normal range in healthy, obese adults and children [77, 78]. Therefore, BMI does not figure in the normal predicted equation of FEV1 and FVC. On the other hand, studies have shown that increasing waist hip ratio, which is a marker of thoracoabdominal obesity, has negative impact on FEV1, FVC, and FEF25-75%, and with every percentage increase in body fat the FEV1 and FVC may decline by 10–15 mL [67, 79]. This suggests that increasing adiposity has potential to induce extra half to three fourth of the normal lung function decline, along with normal lung function decline associated with age and height. This calls for a pertinent consideration of acquisition of body fat mass in

development of normal predicted equations of spirometric lung volumes.

Bronchodilator reversibility and diurnal peak flow (PEF) variability are hallmark of asthma diagnosis. There are some studies which show that obesity is associated with bronchodilator reversibility and PEFR variations in populations. In a study by Castro-Rodríguez et al. girls who became obese after age of six had significantly larger height-adjusted post-bronchodilator FEV1 response and higher prevalence of peak flow variability than children whose BMI level did not change or decreased after age six [25]. In another study, Hakala et al. showed that with decrease in BMI from 37.2 (3.7) to 32.1 (4.2) kg/m^2 the diurnal PEF variation declined from 5.5% (2.4) to 4.5% (1.5), and day-to-day variation declined from 5.3% (2.6) to 3.1% (1.3) in adult asthma patients [80]. What is intriguing is that the obesity related asthma lacks eosinophilic inflammation component [81, 82] and is poorly responsive to steroids [83–85] which is unlike allergic asthma. However, there is some evidence to suggest that adipokines can enhance blood IgE levels and airway smooth muscle contraction similar to what has been demonstrated in allergic asthma [86].

4. Obesity Related Changes in Static Lung Volumes and Its Role in Development of Airway Resistance

The abdominal adipose tissue imposes impedance to diaphragmatic contraction and flattening. This generates an inspiratory load and restricting forces on the lungs to optimally inflate and deflate during tidal respiration [87]. The thoracic and subpleural fat may also restrict the ribcage movements imposing additional restrictive forces on the lungs. These alterations in thoracic mechanics cue towards reductions in lung volumes and lung compliance in obese subjects. Adiposity elucidates exponential association with reducing lung compliance [88–90], perhaps due to obesity related increase in pulmonary blood volume, or obesity induced restriction force related closure of collapsible airways and atelectasis, or increased alveolar surface tension [78] (Figure 1). On the other hand, vital capacity (VC) and total lung capacity (TLC) are not significantly altered in obesity. A marginal 20–30% reduction in TLC has been documented with moribund obesity [78, 91–94].

Over weight and obesity is known to reduce functional residual capacity (FRC) [91]. Sutherland et al. [95] have shown that with each increase in 1 kg body weight can cause an average reduction of FRC of 28–30 mL, however FRC reduction was primarily associated with thoracic and abdominal adiposity, suggesting a plausible interdependent role of fat distribution in two truncal sites in reducing lung volumes. A reduced FRC in obesity reflects decreased respiratory system compliance (Figure 1). FRC is volume of the air in the lung during end tidal expiration during which the inflationary and deflationary forces in the lungs are at equi-pressure point, and there is no movement of air in the respiratory system. It is a sum of expiratory reserve volume (ERV) and residual volume (RV). RV is well preserved in obesity, or may be slightly elevated [92, 94, 96, 97]. Therefore a reduced FRC in obesity is primarily an attribute of reduced ERV. Studies have shown increasing BMI can generate an exponential reduction in FRC and ERV [88, 91, 92]. Low ERV in obesity suggests occurrence of tidal breathing close to RV in distal high resistance airways, such as noncartilaginous small membranous terminal and respiratory bronchioles and alveolar duct, in obese populations (Figure 2). There is a pertinent linear direct relationship between FRC and airway resistance and inverse linear relation with airway conductance [72, 74, 98, 99]. Studies have shown that high respiratory resistance in obesity normalizes on correction with lung volumes [72, 74, 98, 99]. Ofir et al. [100] showed that obese women had significantly lesser FRC and higher percentage of tidal volume which encroached on maximal flow loops at rest compared to normal weight individuals. However, the same study also showed that exercise induces dynamic increases in FRC which attenuates progressive expiratory flow limitation in obese subject. Impulse oscillometry (IOS) studies in obese subjects elucidate that obesity enhances frequency dependence in the airway resistance and increases lung reactance, suggesting that obesity states primarily affects the small airways and impart elastic load on lung mechanics [101, 102]. Oppenheimer et al. [102] showed that excess body weight resulted in enhanced resistance and reactance in the distal airways which reversed after bariatric surgery. High resistance breathing induced by reduced FRC could increase the asthma symptoms, cause treatment refractoriness, and induce a difficulty to treat asthma state. The noncartilaginous small membranous, terminal and respiratory bronchioles, and alveolar duct collapse at low FRC, suggesting that these airways may close during normal tidal breathing in obesity [90, 103, 104]. Tidal airway closure occurs when the closing volume exceeds the FRC. Therefore, obesity can generate a state of cyclic opening and closing of the airway during normal breathing pattern [105]. This recurrent opening and closing of airways is known to trigger epithelial necrosis and sloughing in the membranous and respiratory bronchioles and rupture of alveolar-bronchiolar attachments and increased leucocytes in the alveolar septa in the animal models [106, 107].

A chronic presence of low FRC could also remodel the airways; however, there are no studies which have probed direct changes in the airways of obese humans. There is some evidence to show that despite improvements in lung volumes and reduction in asthma symptoms after weight loss, there is no improvements in volume adjusted airway calibre. This cues towards probable obesity induced remnant of remodelling changes in the airways [78]. However, this can be proved only by carefully designed longitudinal studies. Studies in normal weight subjects have shown that prevention from deep inspiration manoeuvre can increase airway resistance, which does not revert even after reinstating deep inspiration manoeuvre [108–110]. This means that due to chronic restriction in lung movements and reduction in deep inspiration sighs associated with obesity [78], the airway resistance may lose its FRC dependent component over a durational period [97, 111]. The airway smooth muscle has property to adapt to shorter lengths in order to enhance its force generating ability during low lung volume states [112]. This may occur either by plastic adaptation or changes

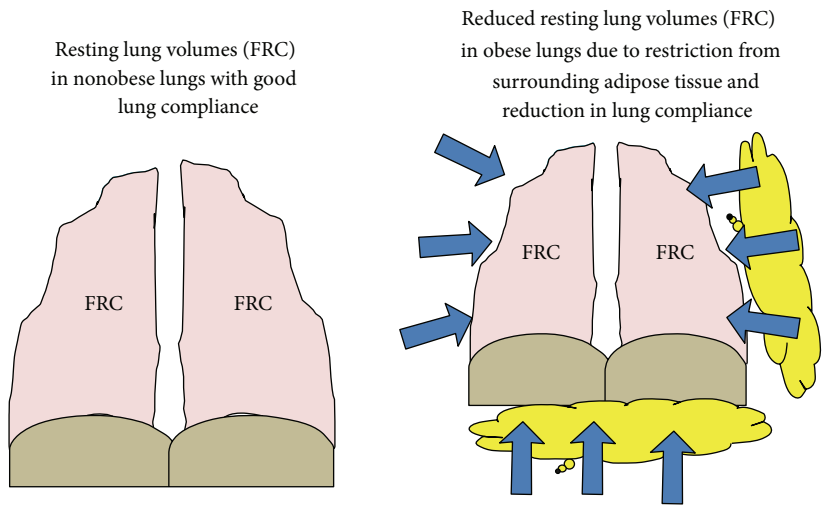

Figure 1: Adiposity resulting reduction in lung compliance and Functional Residual Capacity (FRC).

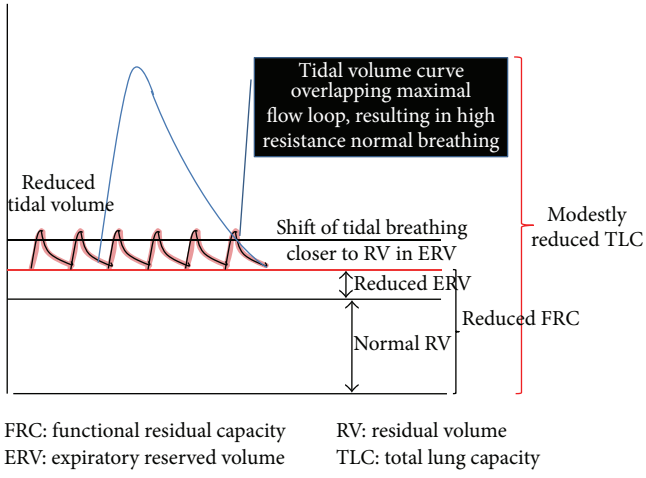

Figure 2: Obese lung tidal breathing volume graph.

in metabolism of actin and myosin. The smooth muscle contracture apparatus constitutes actin-myosin interaction which promotes a latched-in state [112] (Figure 3). The fluctuation forces of inspiration and expiration imposed by tidal breathing disengages the latched-in state and cause smooth muscle relaxation. Severe obesity is usually associated with reduced tidal volumes with rapid and shallow breathing pattern which further enhances with exercise [78, 91, 94]. Therefore obesity constitutes a state in which the tidal breathing fluctuation forces are inadequate to break the latched-in state of actin and myosin filament. This may result in airway narrowing and increased airway resistance. However, it is also important to mention that in mild-moderate obesity tidal volumes and frequency of deep inspiration remain in normal range [100, 113–115]. Therefore there is a possibility that lung functions may not be altered until late obesity in some cases.

5. Obesity and Airway Hyperresponsiveness (AHR)

Airway hyperresponsiveness (AHR) is the cardinal pathophysiology of asthma. Its absence rules out asthma in clinical practise. Unlike obesity and asthma associations, obesity and AHR have not demonstrated any particular epidemiological trends, therefore role of obesity in AHR modulation or vice versa remains largely inconclusive [6, 8]. The effects of weight loss on AHR are also not clear. However there are few large population based cross-sectional and prospective studies which largely indicate a positive link between AHR and obesity [16, 116–118]. There is an evidence to suggest that the incidence and prevalence of AHR increases in obese and underweight population, and its BMI relational graph depicts a U shape association with AHR [16, 117]. Sharma et al. [119] demonstrated that each increase in BMI by 1 kg/m^2 is associated with a 3.1% increase in AHR risk (95% CI 1.01–1.05). There is also some evidence to suggest that obesity may reduce threshold of AHR to potential asthma triggers. The mouse model studies have shown an exaggerated response to methacholine, which enhances further on ozone exposures, independent of lung size, ventilation rates, and satiety hormones, in genetically obese mouse models (ob/ob) [5, 7]. In the humans Alexeeff et al. [120] have shown that there is an equal decline in FEV1 in obese subjects and subjects with underlying AHR on exposures to ozone. Increased ventilation state triggered by increased oxygen demand associated with obesity could cause inhalation of large doses of air pollution in obese versus nonobese individuals. This then can incur more pollution related lung damage [121]. There is also some indirect evidence to suggest that obesity effects on AHR are more prominent prior to asthma development which diminish postasthma development [6–8]. The possibility of this could be linked to a population based study in 1725 adults by Sood et al. [122] which showed that BMI increases AHR in nonasthmatic subjects and not in asthmatic subjects.

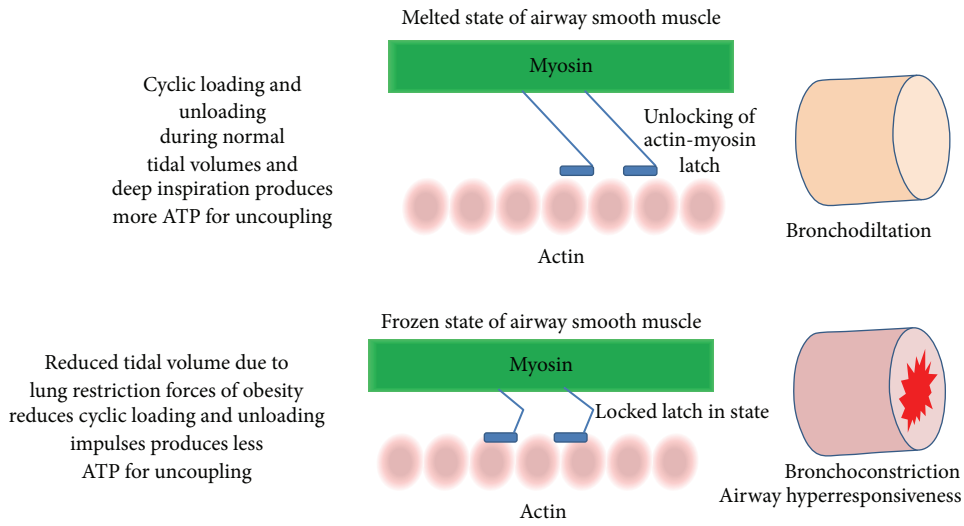

Figure 3: Actin-myosin mechanism of airway narrowing and airway hyperresponsiveness (AHR) in obesity.

Further, there is no particular gender predilection to the obesity-AHR link [6]. Huang et al. [118] studied AHR in 1459 subjects and showed positive relationship between AHR and BMI only in girls. Chinn et al. [116] evaluated 11,277 European adults and showed that AHR increased with BMI in men but not in women. Jang et al. [123] studied prevalence of methacholine hyperresponsiveness in 677 Korean children and showed an increased AHR in obese boys but not in obese girls. However, data from large population based studies suggest equivalent risk between obesity and AHR amongst both genders.

The mechanism of increased AHR in obesity is not clearly elucidated. There is a possibility of potential involvement of mechanical factors associated with low lung volumes as discussed previously. The animal model studies indicate absence of cellular inflammation in the lungs of unchallenged mice; however, there is increased pulmonary oxidative stress similar to what is seen in asthma [6]. Further, the enhanced AHR in obesity could also be linked to increased production of adipokines such as TNF-α, IL6, IL-8, monocyte chemoattractant protein-1, complement proteins, acute phase moieties, leptins and adiponectins from adipocytes and adipose macrophages [6]. It is now increasingly realised that obesity is a state of low grade systemic inflammation which can activate inflammation at sites distant to adipose tissue. Adiponectin is a hormone which is reduced in obesity which has shown to attenuate AHR, eosinophils, and TH2 cells in the lungs of the animal models [6–8]. Another adiposity related hormone, leptin, in concert with other inflammatory agents, has an ability of enhancing AHR. Leptin concentration is 4–6 times higher in severely obese versus nonobese human subjects [124, 125]. However, leptin induces a Th1 type of inflammation rather than Th2 type allergic asthma response [126, 127].

There are also various studies suggesting absence of link between obesity and AHR. Here it is important to mention that 8–12% of the general population may have underlying AHR [128]. Also, there are numerous environmental, genetic, and epigenetic influences on AHR which may conceal any additional effect of obesity [6, 129]. This mandates large sample size requirement in order to probe any AHR-determinant associations in epidemiology studies. The overview of obesity AHR studies in humans indicate that most absent-link studies constitute relatively smaller population size [6] compared to the positive link studies [6, 16, 116]. Inadequacy of appropriate sample size could have negated obesity effects on AHR. Further, most negative studies have primarily emerged from Australian and South American regions [52–55]. A study from Chile [55] has even demonstrated an opposite link between obesity and AHR in population (OR 0.93, 95% CI 0.89–0.97). This calls for a possible geographical-regional, environmental, dietetic and genetic heterogeneity factors to this link. Studies in genetically similar animal models have consistently demonstrated positive obesity and AHR associations [5]. Animal model studies have also shown that obesity-AHR has durational component such that mice with longer duration of obesity have higher risk of developing AHR compared to mice with recent onset obesity [29, 129–134].

Further, fall in FEV1 may not be a sensitive measure to study AHR in obesity. Obesity related restrictive forces are more dominant in the smaller airways. Studies have reported small airway closure in the lower (dependent) region in the lungs of obese individuals [78]. This could redistribute the tidal volumes to other airways, which would then receive enhanced tidal volume proportions that could induce dilatation in the airways [135]. FEV1 may not be an appropriate measure to evaluate the complexity of these heterogeneous alterations in patency of bronchopulmonary tree. On the other hand, markers of small airway flow rates (FEF25-75) and small airway resistances could be more relevant in this case. Both adults and children demonstrate obesity related reductions in FEF25-75 compared to lean subjects [5–8]; reduced FEF25-75/FVC has been regarded as marker of increased hyperresponsiveness [136]. Recently, Salome et al. [137] showed that in obese individuals, the only parameter which significantly changed on bronchoprovocation was airway reactance which is a measure of inertive and elastic

properties of the lung and has been shown to be the marker of transpulmonary resistance.

6. Clinical Implication of Obesity in Asthma

Asthma is primarily managed by inhaled corticosteroids (ICS). However if asthma control is not achieved by ICS, inhaled long-acting b2-agonists (LABA) or other medications may be used as add-on therapy. Intriguingly obesity impinges a relative refractoriness to asthma therapies, and it imposes a state of uncontrolled asthma despite adequate treatments [83, 84]. Boulet et al. [83] had shown that obese asthmatics are less likely than the nonobese asthmatics to achieve asthma control with fluticasone or fluticasone plus salmeterol. However, the cause for steroid unresponsiveness and poor asthma control remains unclear. Further, there is some evidence that treatment unresponsiveness is relatively lesser for leukotriene antagonists in obesity [85].

The reason for poor response to asthma treatment can be associated with increased systemic inflammatory state in obesity, but the evidence suggests that the intensity of lung inflammation obese asthmatic is lesser than that of lean asthmatics. Studies have demonstrated an inverse relationship between BMI and pulmonary eosinophils [81, 82] Data from animal models of allergic asthma have shown less eosinophils and BAL lymphocytes in obese mice versus nonobese mice [82]. There is also some evidence to suggest reduced mitogen and cytokine T-cell response in obese subjects [138–140]. Therefore it can be assumed that obesity induces a pauci-immune type of asthma. This asthma phenotype demonstrates relative steroid resistance. A recent study has shown that weight reduction with intervention such as bariatric surgery can significantly improve asthma control and treatment responses in asthma, but increase CD4 lymphocytes and their cytokine secreting potential [141]. This suggests that weight reduction can induce an inflammation response in the lungs which may revive steroids responsiveness. However, this needs to be evaluated in proper clinical trials.

Larger role of mechanical restriction resulting in altered biophysics of lungs to produce a treatment resistant asthma cannot be undermined. The acute and chronic response improvements in asthmatic conditions after weight reduction interventions suggest pertinent role of mechanical restriction forces and altered lung physiology in causing increased treatment refractoriness, poor asthma control, and exacerbation proneness despite adequate treatment in obese populations [142–155]. The treatment modality of obesity related asthma, therefore, should also include weight reduction strategies along with conventional asthma therapy. Treatments which assist in reducing obesity, such as laparoscopic adjustable gastric binding, silastic ring gastric bypass, vertical banded gastroplasty, biliopancreatic diversion with duodenal switch, lap band, weight loss with structured programmes, and low calorie diets have shown to significantly improve quality of life, reduce asthma severity scores, improve asthma symptoms, reduce number of hospitalizations, reduce use of asthma medications, and induce full remissions in obese asthmatic patients [142–155]. However, therapeutic benefits of weight loss have been somewhat equivocal in regards to improvements in AHR in asthma.

Exercise could be an intriguing intervention in obese asthmatics. Along with potential of reducing weight, exercise may generate deep inspiration and tidal volumes impulses to assist in unlatching actin/myosin latch-in phase and reverse bronchoconstrictions. Reduced physical activity is known to antedate asthma and broncho-hyperresponsiveness [40, 41]. Exercise, on the other hand, can reduce expiratory flow limitation in a dose response manner in obese individuals [100]. Therefore regular exercises along with anti-inflammatory treatments could be an ideal intervention in obese asthma; however, longitudinal studies would be more enlightening.

7. Conclusion

Obesity associated restricted lung mechanics induces series of biophysical effects in the lungs which are known to alter lung physiology, such as reduce lung volumes, increased small airway resistance, induce bronchodilator reversibility, induce peak flow variability, and enhance broncho-hyperresponsiveness, which are conducive to development of asthma. The obesity related asthma has poor response to treatment and encompasses gambit of poorly controlled asthma phenotype. However, it is still not known that whether these altered lung physiologies are accompanied by structural pathologies of the lungs particularly airway remodelling. Properly designed studies are mandated to investigate structural changes in the lungs associated with body fat mass and long-term and short-term beneficial effects on the anatomy and physiology of the lungs with reduction in adiposity.

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