

The Effects of Obesity on Lung Physiology, the Prevalence and Severity of Chronic Pulmonary Diseases, and Inhalation Treatment

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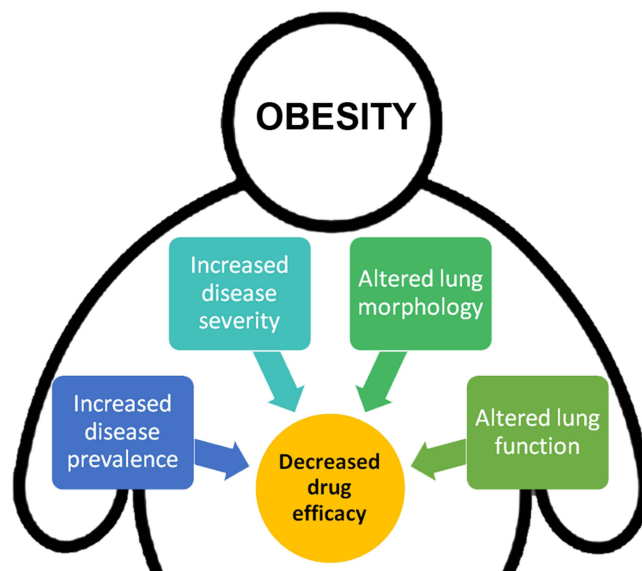
Abstract: Obesity itself induces macroscopic, microscopic, and functional changes in the lungs, potentially making obese individuals more susceptible to acute and chronic pulmonary diseases. Apart from direct contribution to the course of the disease, obesity-induced alterations of the respiratory tract may influence the delivery and efficacy of inhaled formulations. The review examined obesity-induced changes in healthy lungs and the link between obesity and the prevalence and severity of chronic respiratory diseases. Fat accumulation at the tissue and cellular levels, as well as an increased thickness of the smooth muscle layer and an increase in the extracellular matrix, caused a reduction in lung compliance, resistance, reactance, and lung volumes. Conversely, airway hyperreactivity and closure increased, and ventilation/perfusion mismatch was observed. Changes in deposition, metabolism, and permeation across the respiratory barrier in obese lungs may alter the availability of inhaled drugs. Obesity-induced lung alterations may in part explain the higher reported doses of the bronchodilators and anticholinergics in obese compared to normal-weight asthma patients. Based on the observed changes, formulations with smaller particle sizes that require lower airflow may be more effective for obese patients with obstructive lung diseases.

Keywords: lung morphology, lung function, drug bioavailability, asthma, COPD, cystic fibrosis

Introduction

The role of obesity for health is an important matter because the prevalence of adult obesity in 2022 has doubled since 1990 and that of adolescents quadrupled.¹ Numerous studies assessed the relation of weight and disease-free years or life expectancy/mortality. According to a large study from the United Kingdom, mortality was lowest at a body mass index (BMI) of 21–25 kg/m² for all-cause mortality and for mortality from respiratory diseases.² Obesity in this article was defined as a body mass index (BMI) greater than 30 kg/m², and underweight was defined as a BMI less than 18.5 kg/m². The authors reported that the life expectancy of obese patients with respiratory diseases was 4.2 years shorter for men and 3.5 years shorter for women at 40 years of age. Underweight men with respiratory diseases lived 3.5 years shorter, while underweight women lived 4.5 years shorter. The relationship between obesity and mortality risk was described as J-shaped. Other studies have reported a U-shaped relationship between BMI and the risk of dying from respiratory disease.^{3–5} Specifically, the relationship between BMI and mortality in COPD patients was U-shaped.⁶ Unlike a U-shaped association, where the risk is high at both ends, the risk in a J-shaped association is initially low and increases sharply as the variable increases. BMI is not a universally accepted parameter for obesity because it includes both lean and fat tissue, and lean mass (eg muscle) has in general a positive effect on health, whereas visceral fat negatively affects health. When using waist circumference (WC) as indicator for the amount of thoracoabdominal (visceral) fat, a U-shaped relationship between death from respiratory diseases and WC was observed.⁷ Only WC, and not BMI, showed a statistically significant positive association with deaths from lung cancer and chronic respiratory disease.⁸ The last parameter, for which associations to mortality were studied, is the waist to hip ratio (WHR). The WHR

Graphical Abstract



in a population comprising 20–75-year-old individuals showed a J-shaped relationship to all-cause mortality⁹ but experts believe that also the WHR is not an ideal parameter because in gynoid obesity excess body fat may be present although the WHR is below 0.8.¹⁰ Since studies evaluating the influence of obesity on lifetime do not take into account that body weight may have changed during the observation period, it is also possible that persons have normal weight at death due to weight loss induced by disease.¹¹ Furthermore, the importance of obesity as a risk factor for mortality decreases with age and the onset of obesity is important. Later obesity onset reduced mortality compared to early onset. One recent study concluded that stable body weight compared to unintentional weight loss >5% in >60 years old women was a good indicator to reach an age of ≥ 90 years.¹² Differences in age, sex, smoking, body shape, and comorbidity between the studies may also contribute to controversial conclusions on the role of obesity in mortality.

Obesity may not only influence the prevalence and severity (mortality) of chronic pulmonary diseases, but it could also affect treatment efficacy. Pulmonary delivery has several advantages as non-invasive administration form. The large surface area and the thin air-blood barrier enable fast drug delivery at high concentration in the lung. Other advantages include decreased metabolism increasing drug availability and lower systemic toxicity. Despite the potential for high blood levels, pulmonary drug delivery compared to oral delivery is rarely used for systemic treatment.¹³ Exubera, a spray-dried insulin powder, was withdrawn from the market just two years after its release. The improved product, Afrezza, was launched in 2014, but experts estimate that the chances of inhaled insulin obtaining a high market share are poor.¹⁴ Therefore, oral inhalation is mainly limited to the treatment of obstructive pulmonary diseases.

It is hypothesized that obesity-induced lung alterations may affect the availability of drugs used to treat pulmonary diseases. To this end, the review covers obesity-induced changes in lung morphology and function, the association with the prevalence and severity of chronic pulmonary diseases, and the implications for inhalation treatment.

Lung Changes in Obesity

Obesity induces alterations in lung architecture at the macroscopic and microscopic levels. The functional consequences of these alterations are described in the following sections.

Macroscopic Changes

Changes in the respiratory system by obesity occur at morphological level and are linked to the altered physiology. Physiological changes, on the other hand, induce or worsen the morphological changes. Fat accumulation in chest and abdominal cavity are changes visible at the macroscopic level (Figure 1a). Dysanapsis is another common finding in lungs of obese individuals.¹⁵ It describes a mismatch between airway caliber and lung size: too small of airways for the amount of lung tissue present. This results in normal forced expiratory volume in the first second (FEV1) and elevated forced vital capacity (FVC) values, as well as a reduced FEV1/FVC ratio.¹⁶ Furthermore, thickening of the airway walls by increased adipose tissue can be seen. Studies in porcine lungs showed that adipose tissue continues along the conducting airways from the trachea to subsegmental bronchi.¹⁷ Elliot et al reported that adipose tissue area in the conducting airways of human lungs correlated with the BMI.¹⁸

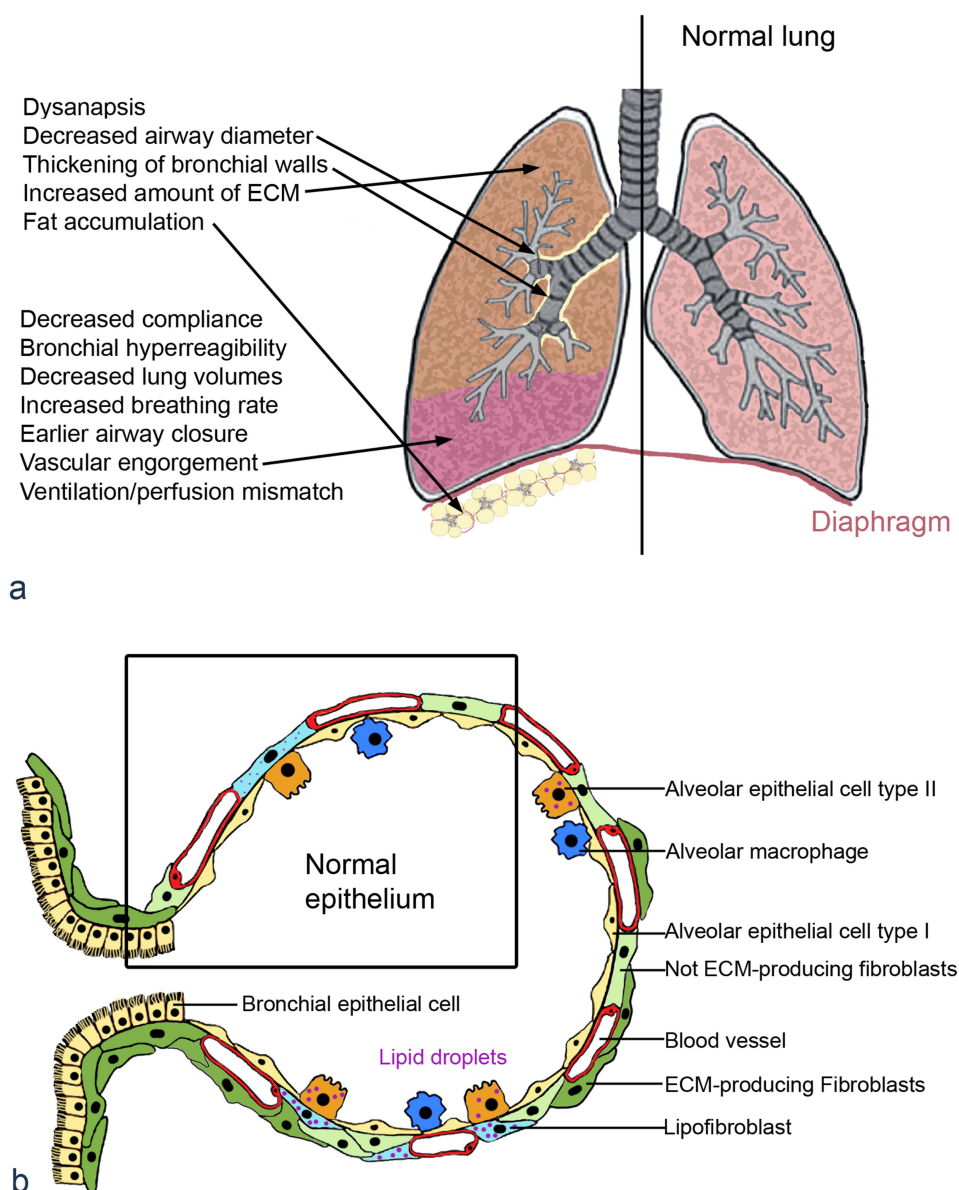


Figure 1 (a) Macroscopic changes in the lungs of obese individuals are smaller airways related to lung size (dysanapsis), decreased airway diameter, thicker bronchial walls by the accumulation of adipose tissue, increased extracellular material (ECM), and accumulation of adipose tissue below the diaphragm. Vascular engorgement can also be seen. (b) In the alveoli of obese patients, microscopic analysis shows that alveolar epithelial type II cells and alveolar macrophages accumulate lipid droplets. Lipofibroblasts contain higher than normal amounts of lipid droplets, and the number of ECM-producing fibroblasts is increased.

Microscopic Changes

Structural differences at the microscopic level are most obvious in the respiratory airways (alveoli) (Figure 1b). Fibroblasts and alveolar epithelial type II cells incorporate lipid droplets. The lipid-containing lipofibroblasts stimulate surfactant production, type IV collagen in the basement membrane and host defense by leptin secretion.¹⁹ Lipofibroblasts serve as additional storage for lipids in obesity and may transdifferentiate in the lungs of morbid obesity into myofibroblasts.²⁰ These cells produce an excess of extracellular matrix (ECM), which is part of the airway remodeling, and can lead to pulmonary fibrosis.

Increased fat content in the lungs of obese rats resulted in a higher number of alveolar macrophages rather than by accumulation of lipid droplet in existing macrophages.²¹ Changes in immune cell number and of cytokine levels in lungs of healthy obese individuals have been reported in mouse models but not confirmed in human lungs.²² Vascular engorgement (increased pulmonary blood volume) causes transudation and thickening of the alveolar-capillary membrane.²³

Cellular changes occur in the conducting airways. On the one hand, an increase in thickness of the smooth muscle layer is observed. On the other hand, the bronchi and bronchioles demonstrate decreased mucociliary clearance (MCC). MCC describes the mechanism by which the cilia of nasal and bronchial epithelial cells propel a mucus layer across the epithelial surface to remove inhaled particles and pathogens from the lungs.²⁴ Down-regulation of cilia-related genes was identified as cause for the decreased MCC in lungs of obese mice.²⁵

Mechanisms Leading to Airway Remodeling

Leptin, produced in adipose tissue, appears to play an important role in the remodeling of the airways in obese lungs. In C57BL/6J mice, an intranasal challenge with house dust mite allergen combined with subcutaneous injection of leptin increased lung fibroblast invasiveness and lung collagen expression, enhancing lung resistance.²⁶ Another study showed that leptin enhances the production of inflammatory mediators and slightly elevates the expression of smooth muscle markers in human fibroblasts.²⁷ The secretion of leptin is stimulated by stretching of the alveolar wall, which may occur to a greater extent in dysanapsis.²⁰

Mechanism Leading to Increased Thickness of the Smooth Muscle Layer

It was hypothesized that increase of the smooth muscle layer in obese individuals is caused by the constant breathing at low functional reserve capacity (FRC) in obesity, which induces shortening of the smooth muscles and adaptation for greater muscle strength at short length.²⁸ According to another hypothesis, actin-myosin bridges are formed and not disrupted resulting in muscle stiffening. Hypertrophy and hyperplasia of airway smooth muscles by obesity was mainly observed in combination with asthma, where an important role of high mobility group box protein 1 (HMGB-1) was identified. Intracellular HMGB1 regulates gene transcription, whereas extracellular HMGB1 triggers and promotes inflammatory and immune responses. The expression of HMGB1 was twofold higher in the adipose tissue of obese individuals than in that of normal-weight individuals.²⁹ HMGB1 increased smooth muscle thickness in a murine asthma model.³⁰ The underlying mechanism was demonstrated to be the stimulation of smooth muscle cell proliferation through RAGE receptor activation and the ERK/NF- κ B signaling pathways.³¹ Furthermore, the protein favors epithelial-mesenchymal transition by reducing the expression of tight junction proteins.³²

Functional Consequences

Effects on Breathing

Accumulation of fat in the chest and abdominal cavities increases pleural pressure, which limits the excursion of the rib cage and diaphragm. In combination with dysanapsis, fat decreases lung compliance (expansibility) in obese individuals.¹⁵ This further increases the work of breathing and decreases the energy stored for passive exhalation. Airway resistance describes frequency-independent friction through the airways, while airway reactance represents inertial and elastic forces and is frequency-dependent. Therefore, obesity-induced morphological changes result in increased resistance and decreased reactance. Inspiratory and expiratory muscle strength were differently reported in studies. Whereas one study reported strength within the normal boundaries, another indicated an increase in muscle

strength in morbidly obese patients.^{33,34} Endurance (the ability of inspiratory muscles to sustain repeated contractions against resistance for an extended period) was reduced compared to normal-weight persons.³⁵ It appears that both inspiration and expiration time are decreased to achieve the increase from 10 to 12 breaths per minute in normal subjects to 15.3 to 21 in obese individuals.³⁶ The increased respiratory rate (number of breaths per minute) compensates for the decreased volume inhaled and exhaled with each respiratory cycle (TV). As result, normal to increased minute volumes were reported in supine position.^{37,38}

Effects on Airflow and Gas Exchange

Thickening of the smooth muscle layer and narrowing of the airways in obesity leads to increased airway hyperreagibility (AHR), which describes the higher contractibility of the small airways. The link of obesity to AHR was reported in several large studies and is associated with decreased airway diameter.²⁸ In addition, subtle inflammation may play a role. However, in the lungs of healthy obese individuals, no increased sensitivity to metacholine stimulation was seen.³⁹

Airway closure is the point during the respiratory cycle when small airways (bronchioles) close off and stop conducting air. This is increased in obesity and more prominent in the paradiaphragmatic region than in the upper regions.⁴⁰ Therefore, more ventilation occurs in the apical regions of the lungs. Due to gravity, perfusion is greater in the lower lung zones and a ventilation/perfusion mismatch results.²⁸ Dysanapsis and AHR in obesity result in decreased tethering forces for expiration and cause obstruction.⁴¹ The decreased tethering forces are explained by the fact that the parenchyma surrounding the small airways experiences greater forces, which may lead to disruption of alveoli.⁴² This favors emphysema development in chronic obstructive pulmonary disease (COPD) and asthma.

Finally, thickening of the alveolar-capillary membrane may lead to airway dysfunction because the gas exchange is hindered by the longer distance between air and blood.²³

Total volume (TV), inspiratory and expiratory reserve volume (IRV and ERV), FRC, and vital capacity (VC) are used as indicators for lung function. IRV and ERV are the additional volumes that can be inspired/expired at the end of a tidal inspiration/expiration. FRC refers to the volume remaining in the lungs after a normal, passive exhalation, and VC is the total amount of air exhaled after maximal inhalation. Residual volume (RV) is the amount of air that always stays in your lungs to prevent the alveoli from collapsing. Changes in these volumes in obese lungs are shown [Figure 2](#). Reduction in total lung capacity (TLC) is only obvious in morbid obesity.^{43–46} FEV1 is generally reduced due to the decreased airway diameter.

In summary, obesity leads to a decrease in lung compliance and reactance, as well as a decrease in endurance and most lung volumes. Meanwhile, AHR, airway closure, and respiratory rate increase.

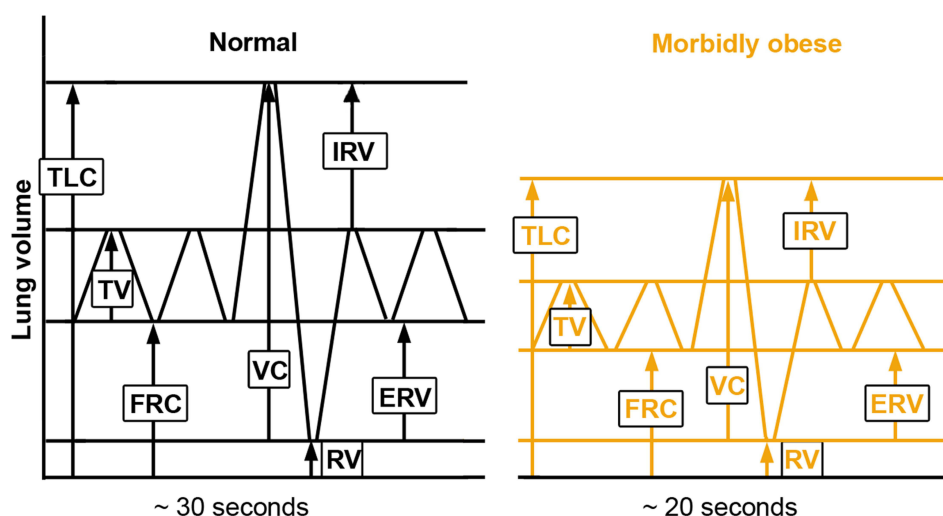


Figure 2 Obesity-induced changes of lung volumes and tissue. Total lung capacity (TLC), functional reserve capacity (FRC), tidal volume (TV), vital capacity (VC), inspiratory reserve volume (IRV), expiratory reserve volume (ERV) are decreased, while residual volume (RV) remains constant.

Syndromes Associated with Obesity

The combination of increased upper airway resistance, fat deposition, and elevated intra-abdominal and pleural pressures leads to hypoventilation syndrome (OHS).⁴⁷ This syndrome occurs in 31% of individuals with a BMI greater than 35 kg/m² and is associated with decreased FRC, ERV, and TLC. Obese individuals are affected by obstructive sleep apnea (OSA) to a greater extent than individuals of normal weight. Both conditions exacerbate obesity-induced respiratory system alterations and worsen chronic pulmonary diseases. It is proposed that hypoxia, which triggers the release of inflammatory cytokines (IL-6, TNF- α , and C-reactive protein), is the main mechanism of airway and pulmonary vasculature damage. OSA induces microvascular endothelial dysfunction and increases pulmonary artery pressures and right ventricular afterload.⁴⁸

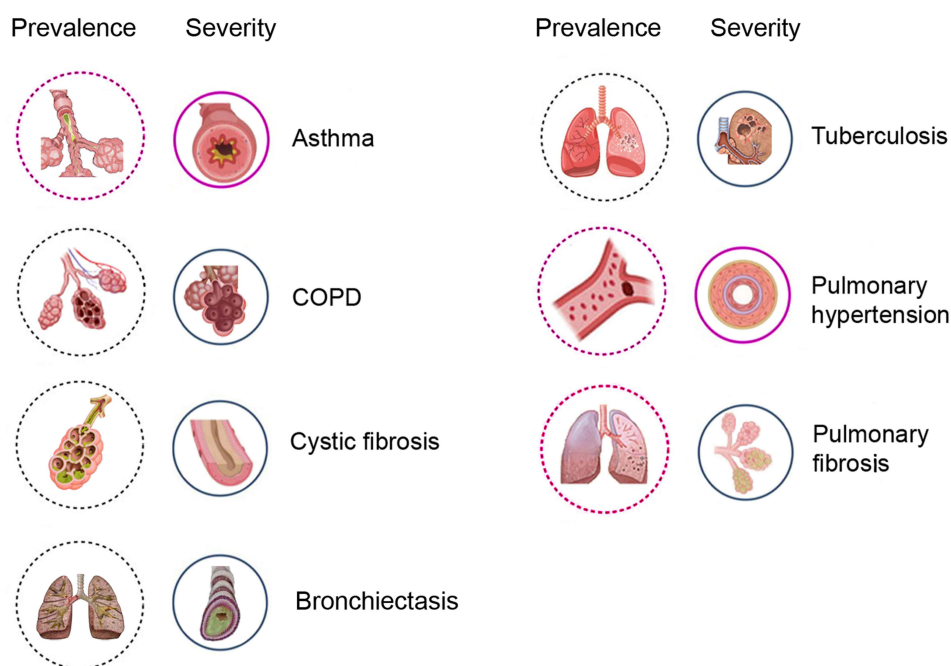
Association of Obesity and Chronic Respiratory Lung Diseases

The obesity-induced lung changes have consequences on acute diseases (vulnerability to infections). Both infections of the upper (tonsillitis, nasopharyngitis, sinusitis) and of the lower (bronchitis, pneumonia) respiratory tract occur more frequently in obese than in normal-weight individuals.⁴⁹ Typical examples are respiratory infections caused by the bacterial strains *Streptococcus pneumonia* and *Klebsiella pneumonia* and by the viruses like respiratory syncytial virus, influenza A and severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). Frequency of viral infections, pneumonia, and acute respiratory distress syndrome (ARDS) was linked to obesity.⁵⁰ Also, markedly more obese than normal-weight patients with SARS-CoV-2 infections were admitted to the intensive care unit (ICU) (eg,^{51,52}). Intuitively, it would be expected that this would also lead to higher mortality. However, lower mortality of obese patients with ARDS, COPD, and pneumonia was seen, a phenomenon called “obesity paradox”.⁵³ Similar protection against mortality was observed for a broad panel of diseases, such as stroke, thromboembolism, type 2 diabetes mellitus, hemodialysis, critically ill patients and cardiovascular surgery.⁵⁴ The reasons for this are not exactly known. Altered immune responses, increased fat and muscle reserves, microbiota changes have been hypothesized.⁵³

To identify the effects of obesity on chronic pulmonary diseases, the prevalence and severity were compared between obese and normal-weight patients. Figure 3 shows the increased prevalence and severity in obese patients.

Asthma

The closest relation of obesity to respiratory diseases was identified for asthma (eg,^{62–64}). Prevalence of adult onset asthma was higher in obese individuals with a BMI >25 kg/m² than in individuals with lower BMI.⁶⁵ Compared to patients with lower BMI, the increase in prevalence was 12.5% in individuals with BMI between 25 and 29.9 kg/m² and 250% among persons with 50 kg/m². Similarly, the severity of asthma was higher among obese individuals because obesity was found to be associated with asthma in a dose-dependent manner. Furthermore, obesity appeared to increase the likelihood of experiencing a more persistent and severe asthma phenotype.⁶⁶ The association was independent of socio-demographic determinants, physical activity, and dietary patterns. One study identified a linear relationship between asthma severity and BMI.⁶⁷ Another study found that high or low BMI was associated with cough, shortness of breath, and dyspnea. It has also been linked to bronchial asthma and COPD.⁶⁸ Asthma in obesity can be differentiated into early onset (EOA) and late onset (LONA) asthma. EOA resembles allergic, eosinophilic Th2-driven asthma and responds to corticosteroids. EOA is accompanied by greater airway obstruction and positively correlated with BMI. The patients had greater AHR and the risk was 4–6 fold higher for hospitalization.⁶⁹ LONA is characterized by Th1/Th17 responses and neutrophilic inflammation and poorly responds to corticosteroid treatment. It affected more women than men, was characterized by lower AHR, more persistent airway remodeling, poorer symptom control and more frequent exacerbations. Obesity is linked to prevalence and severity of both asthma types.^{70,71} Studies also found that obese patients have less favorable response to asthma therapy than normal-weight asthma patients, which may indicate that drug delivery is less efficient in these patients.⁷² The link to obesity was further confirmed by the several studies that reported that weight loss improved asthma severity, AHR, asthma control, lung function, and quality of life (eg,⁷³). Odds ratio for severe asthma (emergency room visits) were higher for obese than for non-obese individuals. To compensate the bias introduced by the measurement of BMI, correlations of asthma prevalence to WC was indicated. The authors reported that increased values were linked to asthma in women and men⁷⁴ and thereby confirmed the association between obesity and asthma.



Parameter: **increased** or not increased in obese patients

Figure 3 Obesity increases both prevalence and severity of asthma and pulmonary hypertension. The icons show the main characteristics of the disease. Asthma with epithelial detachment, mucus gland hyperplasia, subepithelial fibrosis, inflammatory cell infiltration, and smooth muscle hypertrophy.⁵⁵ In chronic obstructive pulmonary disease (COPD) there is inflammation dominated by CD8 lymphocytes, eosinophils, macrophages and from earlier to later stages increasing numbers of neutrophils in all parts of the bronchial tree and pulmonary vasculature and alveolar wall destruction.⁵⁶ Cystic fibrosis caused by the cystic fibrosis transmembrane conductance regulator (CFTR) gene leads to neutrophil-dominant airway inflammation around the airways.⁵⁷ Further goblet cell and submucosal gland hyperplasia is seen. The inflammation pattern differs between the genotypes. In bronchiectasis, dilated bronchi can present in cylindrical, varicose, and cystic forms.⁵⁸ Thickening of the bronchial wall and mucus plugging can be seen in the bronchi. The presence of granuloma with typical morphology at early and late stages is the hallmark of tuberculosis.⁵⁹ Typical histological features include epithelioid differentiation of macrophages and multinucleated giant cells by fusion of several macrophages. In the same lung, granuloma with different morphology can be seen. Pulmonary hypertension primarily affects pulmonary arteries and arterioles and vessels show hypertrophy of the media, fibrosis of the intima and thrombotic lesions. Further, lesions composed of proliferated endothelial cells, smooth muscle cells, fibroblasts, and inflammatory cells at the branching points of the vessels. Lung histology outside of the pulmonary vessels is not much altered.⁶⁰ In idiopathic pulmonary fibrosis the normal lung tissue is interspersed with fibrotic areas of different composition, inflammatory cells and abnormal lung architecture.⁶¹ So-called honeycomb cysts are formed resulting from destructed alveoli.

Chronic Obstructive Pulmonary Disease (COPD)

Unlike asthma, where the association is strong and consistent, the link between obesity and COPD is more complex and influenced by smoking status. COPD patients are often smokers and smokers, on the average, have a lower body weight than non-smokers. Studies from several countries report smoking in COPD in the 30–40% range,⁷⁵ which is considerably higher than the smoking rate in asthma patients. If only non-smokers were studied, a strong dose–response relationship between obesity levels and COPD prevalence was identified with higher BMI correlating to increased COPD risk.⁷⁶ Two studies distinguished between abdominal and general obesity, reporting that abdominal/visceral obesity is associated with COPD.^{77,78} A study investigating the influence of sex found that COPD was associated with both abdominal and general obesity in women.⁷⁹ However, a higher prevalence of COPD in individuals with a low BMI and a smaller WC was also reported.⁸⁰ The role of smoking was not consistently evaluated in the studies, which could bias the evaluation. Another bias was that WC values were a mixture of self-reported and standardized measurements. The link of obesity to COPD severity was found to be not linear and also not consistent. Whereas one study found that obesity was associated with worse COPD-related outcomes,⁸¹ another found that obesity was associated with reduced COPD exacerbations and better lung function.⁸² A third study reported that obese and overweight patients complained more of dyspnea and poor life quality than normal-weight individuals but their lung function (eg FEV1) was better.⁸³

Cystic Fibrosis (CF)

The link between CF and obesity differs from that of the previously mentioned obstructive diseases because patients with CF are more likely to be underweight due to pancreatic insufficiency leading to malabsorption. Digestion of food and absorption of nutrients is decreased and patients are encouraged to eat high fat, high calorie foods. The improved treatment options of CF resulted in a higher life expectancy of the patients and a higher obesity rate of 31.4%.⁸⁴ The meta-analysis based on 9114 patients reported that overweight and obesity were associated with higher FEV1 compared with normal weight. It has been reported that weight gain of undernourished patients improved lung function.⁸⁵ There is no cut-off level for weight but improvement of lung function is minimal for BMI >30 kg/m². Other authors see a problem in the raising of obesity in CF patients and suggest an individual nutrition plan.⁸⁶

Non-CF Bronchiectasis

Although CF may be a cause of bronchiectasis formation, repeated infections and inflammation that damage the airways are more common reasons.⁸⁷ The prevalence and severity of bronchiectasis were reported differently in the studies. In one study, both parameters were higher in obese patients,⁸⁸ whereas in other studies, underweight individuals were more prevalent and presented with more severe symptoms within the bronchiectasis patient group.^{89,90} However, more severe presentations of bronchiectasis in obese patients due to repeated infections have also been reported.^{91,92} Finally, a meta-analysis of 437,851,478 individuals reported that BMI did not significantly affect bronchiectasis prevalence, reflecting the conflicting results of the studies.⁹³

Tuberculosis (Tbc)

The importance of infection links Tbc to the previously discussed chronic pulmonary diseases. However, the association to obesity is quite different because a strong inverse logarithmic relationship between BMI in the range of 18.5–30 kg/m² and incidence of Tbc has been reported.⁹⁴ The authors supposed that lipids interfered with replication of the mycobacteria because mycobacteria containing lipid bodies did not replicate as rapidly as mycobacteria without such lipid bodies. Further, mycobacteria remained dormant in adipose tissue.^{95,96} Both findings support the hypothesis of a negative influence of fat on the infectious potential of the mycobacteria. The studies were performed in high-income countries, which may limit conclusions for other countries. Even obese individuals with type 2 diabetes mellitus had a 70% reduced risk of Tbc,⁹⁷ although, in general, diabetes increases the incidence of concomitant diseases. The association of disease severity with obesity is not obvious because obesity can increase risks of Tbc treatment (eg increased side effects). However, mortality from Tbc was not higher in overweight than in normal-weight patients.⁹⁸

Pulmonary Hypertension (PH)

Unlike the chronic pulmonary diseases described in the previous section, the diseases described in the next two sections are not characterized by obstruction, increased mucus production, or infections. There is a strong association between obesity and prevalence of PH.⁹⁹ Studies on the association of obesity and PH suggest that obesity may influence both PH onset and severity.¹⁰⁰ Parameters that might be implicated include secretion of pro-inflammatory cytokines, leptin-induced endothelial dysfunction and other mediators. Data from animal experiments suggested a prominent role of adiponectin in the protection against PH because adiponectin levels were associated with reduced smooth muscle cell proliferation and decreased levels of inflammatory cytokines. This effect is reduced in obese patients because adiponectin levels are lower than in lean patients. Additional reasons may be hyperuricemia leading to pulmonary vessel dysregulation, fat deposition in the myocardium, and hypoxic vasoconstriction. According to a meta-analysis including 13,987 patients, obesity according to BMI (>30 kg/m²) was linked to longer survival of PH patients in all six studies included in this meta-analysis.¹⁰¹ However, when a differentiation between lean and fat body mass was made, lean mass had a positive and fat mass a negative effect. The effect on survival may also be determined as longer because symptoms occurred earlier in the obese than in the normal-weight population of PH patients.

Idiopathic Pulmonary Fibrosis (IPF)

A Mendelian randomization analysis revealed that increased BMI and WC were associated with a higher risk of IPF.¹⁰² Ectopic and visceral fat deposition may also increase the severity of IPF.¹⁰³ Mechanisms for induction and promotion of IPF were mechanical effects (fibrosis of the diaphragm), generation of oxidative stress (eg ox-low density lipoprotein) and secretion of various inflammatory mediators, such as tumor necrosis factor α (TNF- α), interleukin (IL)-1 α , monocyte chemoattractant protein 1 (MCP-1), transforming growth factor β (TGF- β).¹⁰⁴ In animal models, elevated circulating leptin levels, higher TGF- β 1 expression in the bronchial epithelium promoting epithelial-mesenchymal transition in alveolar epithelial cells, and endoplasmic reticulum stress leading to myofibroblast differentiation with increased collagen production were identified.^{105–107} In contrast to the data that obesity can promote IPF in animal experiments, obese patients in one study showed less advanced fibrosis with a lower mortality rate relative to non-obese individuals.¹⁰⁸ This finding excludes/shakes the hypothesis of an association between IPF severity and obesity.

Potential Mechanisms That Link Chronic Pulmonary Diseases to Obesity

Huang et al identified a causal relationship between visceral adipose tissue and asthma, COPD and IPF at the genetic level using multivariate mendelian randomization.¹⁰⁹ They emphasized the importance of immune processes involving the overproduction of pro-inflammatory cytokines, which promote immune cell recruitment, stimulate fibrosis, and prolong the inflammatory response. Therefore, the chronic low-grade system inflammation seen in obesity can aggravate the pathology. The adipokines leptin and resistin, the cytokines TNF- α , IL-6, IL-1 β and the chemokines MCP-1, RANTES, IL-8, CXCL1, eotaxin exacerbate lung inflammation. Furthermore, alterations in the Th1/Th17 ratio were observed, along with increased tissue remodeling and fibrosis due to the release of TGF- β , IL-6, and TNF- α . Reduced lung function was also reported.¹¹⁰

Treatment of Chronic Respiratory Lung Diseases

Oral inhalation is the dominant treatment modality for asthma, COPD, CF and bronchiectasis.^{111–113} For asthma and COPD, a broad panel of inhalation products containing short-acting (SABA) and long-acting β 2-agonist (LABA), long-acting muscarinic agonists (LAMA), inhaled corticosteroid (ICS), and combinations thereof are available. Therapies for CF (DNase, CFTR modulators, antibiotics) are delivered by nebulizer.¹¹⁴ Inhalation treatment is also used to restore MCC, eradicate *Pseudomonas aeruginosa*, and reduce obstruction in non-CF bronchiectasis.¹¹⁵ The common administration route for other chronic pulmonary disease is oral delivery. This is partly due to the fact that the production of inhalation products is pharmaceutically more challenging and the panel of approved excipients less broad than for oral products.¹¹⁶ Endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, prostacyclin analogues, and prostacyclin receptor agonists are used for oral treatment of PH.¹¹⁷ More recently, first inhalable formulation for PH was approved by the food and drug administration (FDA).¹¹⁸ These include inhaled iloprost, inhaled treprostinil solution and treprostinil dry powder inhaler. The main oral medication for IPF are pirfenidone and nintedanib¹¹⁹ and several nano-based inhaled formulations are in different phases of clinical development.¹²⁰ In Tbc therapy, the standard drugs rifampicin, pyrazinamide, isoniazid and ethambutol are administered by the oral and intravenous route.¹²¹ To avoid the marked adverse effects, pulmonary formulations are being developed but not yet broadly used.¹²²

Effects of Obesity-Induced Lung Changes on Inhalation Treatment

Obesity can influence drug bioavailability of pulmonary formulations on different levels, deposition, permeation across the epithelial barrier and metabolism.

Effects on Particle Deposition

Due to airway narrowing, early airway closure, ventilation/perfusion mismatch, and particle clearance, the deposition of particles is expected to be less homogeneous in obese patients than in patients of normal weight. The narrowing of small airways that occurs at lower lung volumes is hypothesized to cause in part the observed twofold increased resistance of

lungs of obese individuals compared to normal-weight controls.¹²³ Airway narrowing and early airway closure lead to gas trapping and ventilation inhomogeneity.¹²⁴ While conventional respiratory tests (spirometry) showed only mild effects, oscillometric evaluation of respiratory system impedance was a more sensitive¹²⁵ and demonstrated a changed distribution pattern of inhaled medications.¹²⁶ The apical parts of the lungs are better ventilated whereas perfusion is higher in the basal parts of the lung. In normal-weight individuals, deep inspiration and breath holding lead to relatively homogeneous ventilation of all regions of the lungs.¹²⁷ By contrast, obese individuals cannot achieve this to the same extent. This results in a more pronounced ventilation/perfusion mismatch.

Also, elimination of inhaled particles is influenced by obesity. MCC in the bronchi is difficult to determine but nasal mucociliary epithelium is regarded as a mirror image of the bronchial mucosa. The time taken to experience sweet taste at the posterior nasopharynx following the placement of a saccharin crystal in the nostril is an established parameter to determine nasal MCC. In this assay, the time was 7.00 minutes for normal-weight (18.5–24.9 kg/m²), 7.16 min in the overweight (25–29.9 kg/m²) and 5.81 min in the obese (>30 kg/m²) individuals.¹²⁸ Another research group that used a cut-off of 22.9 kg/m² between normal-weight and overweight/obese individuals reported a prolonged MCC (9.77 ± 3.02 min) in the group with BMI of ≥ 23 kg/m² compared to 5.74 ± 2.35 min in the normal-weight group.¹²⁹ Since the WHO defines overweight and obese at BMI ≥ 25 kg/m², a linear correlation of MCC to BMI is unlikely. The studies concord in the finding that MCC is decreased in obesity. The density of ciliated cells decreases significantly from bronchi (17.9 ± 1.6 × 10³) to bronchioles (14.3 ± 2.9 × 10³) in human airways.¹³⁰ Therefore, MCC will have a greater effect on larger airways than on smaller ones, leading to increased particle deposition in the central lung.

Permeation Across the Respiratory Barrier

Permeation across the respiratory barrier is fast compared to other common non-parenteral routes, such as skin and gastrointestinal epithelium because the epithelial barrier (air-blood barrier) measures only around 2 µm.¹³¹ However, the increased thickness of the alveolar-capillary membrane may reduce this positive effect to certain degree.²³ Regarding the permeability of the epithelial lining of the lung, similar effects as for the intestinal barrier have been assumed.¹³² Studies of the intestinal epithelium of obese patients reported decreased tightness of epithelial tight junctions and lower expression of junctional proteins leading to increased permeability. Similar increase in permeability was detected for the pulmonary barrier epithelium of asthma patients with obesity and explained by elevated levels of reactive oxygen species causing inflammation and cell damage. In obese patients with IPF, higher concentrations of plasma proteins in the bronchoalveolar lavage than in healthy individuals were determined as indication for a leakier pulmonary barrier.¹³³ Based on these findings, it can be assumed that the permeation by paracellular transport could be increased in obese patients. It is not expected that the increased permeability has a major effect on bronchodilators, which have molecular weights of ~300 g/mol and cross the healthy epithelial layer by paracellular transport.¹³⁴ However, drug diffusion within lung tissue may decrease due to increased extracellular matrix in obese patients' lungs.²⁰ This is due to the transdifferentiation of lipofibroblasts into myofibroblasts that occurs in the lungs of obese patients.

Metabolism

In addition to absorption, drug availability is determined by metabolism. Most conventional small molecular drugs are metabolized by oxidative enzymes like cytochrome P450 (CYP), flavin-containing monooxygenases, monoamine oxidase, xanthine oxidase/aldehyde oxidase and epoxide hydrolase.¹³⁵ CYP isoenzymes are the most important family of enzymes and account for about 75% of the total human drug metabolism.^{135,136} Drug metabolism by flavin-containing monooxygenases and CYP isoenzymes CYP1B1, CYP2C9, CYP2J2, and CYP3A4 by human alveolar epithelial type II cells is low compared to hepatocytes.¹³⁷ Therefore, the authors of that study concluded that drugs are minimally metabolized when administered by inhalation. The higher number of inflammatory cells seen in the lungs of obese mice¹³⁸ will not affect the metabolism rate of conventional drugs markedly because immune cells contain low levels of CYP isoenzymes.¹³⁹ However, degradation of proteins and peptides may be increased because alveolar macrophages and inflammatory cells contain a variety of proteases.¹⁴⁰ Inhaled peptides, for instance insulin, may have lower efficacy in obese patients due to increased degradation by phagocytes. Since changes in the numbers of inflammatory cells in healthy obese lungs were seen only in mice, this effect can only be speculated.

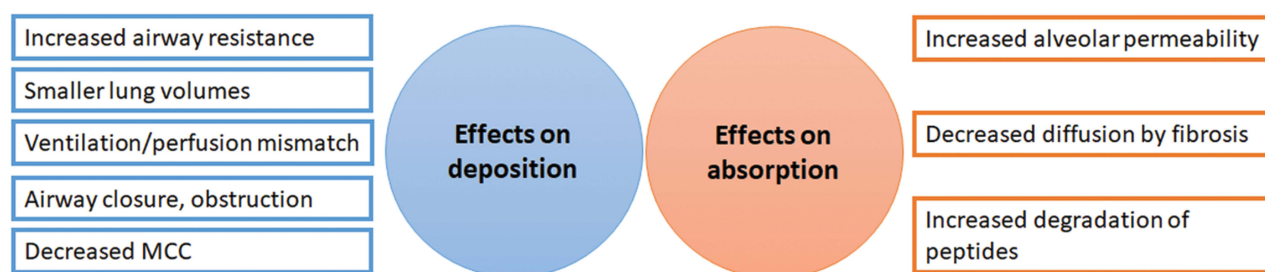


Figure 4 Effects of obesity on drug deposition and absorption in lungs of obese compared to normal-weight individuals.
Abbreviation: MCC, mucociliary clearance.

In summary, smaller lung volumes and increased airway resistance are expected to reduce drug deposition in general. Airway closure and obstruction and ventilation/perfusion mismatch will induce irregular drug distribution. Decreased MCC will further increase the irregular distribution of drugs, delaying the removal of particles from the central regions of the airways. Whereas increased paracellular permeability should not have a great impact on paracellular transport of common inhaled medications such as bronchodilators, decreased tissue diffusion could reduce drug concentration at the target cells. Metabolization of small molecules should remain unchanged, whereas degradation of peptides may be enhanced (Figure 4).

Conclusion

Asthma may be the most appropriate chronic pulmonary disease to show the effect of obesity-induced lung changes in inhalation treatment for the following reasons. Obesity increases the risk and aggravates the course of asthma,¹⁴¹ treatment is mainly by inhalation, and higher use of bronchodilators was reported.⁶² Comparing bronchodilator use is better than comparing inhaled corticoid use because higher corticoid use could be due to the generally lower responsiveness of LONA to glucocorticoid treatment.¹⁴² LONA, also known as T2-low asthma, lacks the typical T2 immune pathway markers, such as IL-4 and IL-13, and is more prevalent in obese patients than in those of normal weight. Obesity-induced changes in lung function and histology could explain why the inhaled bronchodilators but not intravenous treatments (eg monoclonal antibody) are less effective in obese than in non-obese patients. Potential mechanisms include reduced total drug deposition due to small lung volumes, general airway obstruction, and altered drug deposition caused by early airway closure restricting drug access to affected bronchioles and ventilation/perfusion mismatch. Furthermore, fibrotic changes could restrict drug access to the target (smooth muscle) cells.

Based on these considerations, the following may be advantageous:

- i. Reducing weight to improve lung function.
- ii. Adapting inhalation doses to body weight.
- iii. Using formulations consisting of smaller particles for better delivery to peripheral regions of the lung.

Abbreviations

ARDS, acute respiratory distress syndrome; AHR, airway hyperreagibility; BMI, body mass index; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; COPD, chronic obstructive pulmonary disease; CYP, cytochrome P450; ECM, extracellular matrix; EOA, early onset asthma; ERV, expiratory reserve volume; FEV1, forced expiratory volume in the first second; FRC, functional residual capacity; HMGB-1, high mobility group box protein 1; ICS, inhaled corticosteroid; ICU, intensive care unit; IL, interleukin; IPF, idiopathic pulmonary fibrosis; IRV, inspiratory reserve volume; LABA, long-acting β_2 -agonist; LAMA, long-acting muscarinic agonist; LONA, late onset asthma; MCC, mucociliary clearance; OHS, obesity-hypoventilation syndrome; PH, pulmonary hypertension; SABA, short-acting β_2 -agonist; SARS-CoV-2, severe acute respiratory syndrome corona virus 2; Tbc, tuberculosis; TGF- β ,

transforming growth factor β ; TLC, total lung capacity; TNF- α , tumor necrosis factor α ; TV, tidal volume; VC, vital capacity; WC, waist circumference; WHO, World Health Organization; WHR, waist to hip ratio.

Disclosure

The author reports no conflicts of interest in this work.

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