83337_Auto_Edited.docx

WORD COUNT 2241
TIME SUBMITTED 15-MAR-2023 10:05PM
PAPER ID 97650019

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 83337

Manuscript Type: MINIREVIEWS

Implications of obesity and adiposopathy on respiratory infections; focus on emerging challenges

Implications of obesity and adiposopathy on respiratory infections

Ioannis G Lempesis, Vasiliki E Georgakopoulou

Abstract

Obesity is characterized by excessive adipose tissue accumulation, which impacts physiological, metabolic, and immune functions. Several respiratory infections, including bacterial pneumonia, influenza, and coronavirus disease 2019 (COVID-19), appear to be linked to unfavorable results in individuals with obesity. These may be attributed to the direct mechanical /physiological effects of excess body fat on the lungs' function. Notably, adipose tissue dysfunction is associated with a low-grade chronic inflammatory status and hyperleptinemia, among other characteristics. These have all been linked to immune system dysfunction and weakened immune responses to these infections. A better understanding and clinical awareness of these risk factors are necessary for better disease outcomes.

Key Words: COVID-19; influenza; lung disease; immune system; obesity

Lempesis IG, Georgakopoulou VE. Implications of obesity and adiposopathy on respiratory infections; focus on emerging challenges. *World J Clin Cases* 2023; In press

Core Tip: Obesity influences the development and outcome of various respiratory infections. This is mediated in various ways, including through direct physiological impacts on the lungs and airways and *via* the dysfunctional adipose tissue, inducing a low-grade inflammatory status that potentially affects the immune response to certain pathogens. These include, notably, influenza and COVID-19. Clinicians should be aware of these unique challenges in this subset of patients and take preventive and aggressive therapeutic measures as needed.

INTRODUCTION

Obesity is a complex chronic disease linked to increased risk of nearly every chronic condition, including insulin resistance states, diabetes, cardiometabolic diseases, and various types of cancer, overall resulting in poor quality of life and reduced life

expectancy[1–3]. Furthermore, obesity has a significant impact on respiratory health, and this has become even more apparent during the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory coronavirus 2 (SARS-CoV-2)[4,5], as obesity has been associated with an increased risk of infection and unfavorable clinical outcomes in people with obesity that encounter COVID-19[6,7]. However, the burden of obesity on various infectious diseases was already recorded before and independently of the COVID-19 pandemic[8,9].

Obesity has been linked to an increased risk of pulmonary infections, including pneumonia, bronchitis, chronic obstructive pulmonary disease (COPD) exacerbations, and various other viral infections that we will further describe here[10]. Some of the mechanisms by which obesity increases the risk of respiratory infections include changes in pulmonary function, *e.g.*, decreased lung volumes, impaired gas exchange, and secretion mobilization[10–13]. Moreover, mechanical blockage can also be caused by fat deposition in the upper airways[10, 13–15]. Notable obesity appears to affect the immune system through a chronic low-grade inflammatory status[2,16]. Adipose tissue, which increases with obesity, is an active endocrine organ that secretes adipocytokines and other inflammatory mediators[2]. Such substances sustain a low-grade systemic inflammation, potentially impairing the immune system's capacity to combat infections [2,8,16,17].

In this review, we presented the numerous pathophysiological implications of obesity and dysfunctional adipose tissue on pulmonary function, the immune system, and pulmonary infections. We summarized the overall impact of obesity on disease outcome and highlighted various emerging and ongoing challenging infections, including, tuberculosis, COVID-19, influenza, and other bacterial or viral infections. Finally, we explored the impact of obesity on various vaccines and suggest strategies to prevent and treat lung infections in individuals with obesity.

EPIDEMIOLOGY OF LUNG DISEASES IN THE PRESENCE OF OBESITY

Obesity has been associated with a variety of respiratory disorders, notably COPD, asthma, obstructive sleep apnea (OSA), pulmonary embolic disease, and aspiration pneumonia[18]. Several epidemiological studies have reported a relationship between respiratory tract infections and obesity, in particular higher prevalence, disease duration, and mortality[17]. Individuals with overweight or obesity had a higher rate of outpatient visits for acute respiratory infections during influenza season than individuals with normal weight, according to a large cohort study from Canada that examined a variety of acute upper (nasopharyngitis, sinusitis, tonsillitis) and lower (bronchitis, pneumonia, influenza, and other viral infections)[19]. In the United States, comparable results were obtained for the risk of community-acquired pneumonia[20] and chronic bronchitis in children, adolescents, and adults[21,22]. More recently, obesity and diabetes were recorded among the high-risk factors for severe COVID-19[23]. Notably, even though obesity is a significant risk factor for the occurrence of acute respiratory distress syndrome (ARDS) and acute lung injury (ALI), in a recent meta-analysis it was recorded that, as opposed to those with a normal BMI, ARDS/ALI outcomes were more favorable in the individuals in the obesity group[24]. Overall, individuals with obesity are at increased risk of severe infections, delayed recovery, and complications like ARDS or ALI [10,25].

PATHOPHYSIOLOGICAL BACKGROUND

Although the precise mechanisms linking obesity and an increased risk of pulmonary infections remain unknown, several potential factors have been hypothesized and proposed[10,11,15,26]. These are divided into two categories: first, anatomical-functional changes caused by the mechanical impediment of excess adipose tissue, which blunts respiratory processes and contributes to respiratory diseases[11,15]. And secondly, due to the obesity-related adipose tissue dysfunction/adiposopathy resulting in low-grade inflammation, hyperinsulinemia, hyperglycemia, and hyperleptinemia, all of which contribute to a weakening of both innate and adaptive immunity[17,26].

Impaired lung function and related mechanisms

Obesity alters the mechanical characteristics of both the lung and thorax substantially, owing mostly to fat accumulation in the mediastinum and abdominal cavities[10]. These result in a decrease in the compliance of the lungs, thorax, and the respiratory system as a whole[10,27]. Moreover, as adipose tissue accumulates in the thoracic and abdominal cavities, the diaphragm's downward movement and the thoracic wall's outward mobility are restricted[10,28]. This affects the breathing pattern, resulting in a significant decrease in both the expiratory reserve volume and the lung's resting volume, known as functional residual capacity (FRC). The decrease in FRC is related to the degree of obesity[10,29]. Importantly, body fat distribution plays an important role, with abdominal and upper body accumulation being independent of the BMI in relation to the worsening of these parameters [12,30,31]. Obesity frequently causes increased respiratory system resistance, as well as airway restriction and closure, and airway hyperresponsiveness, resulting in unfavorable peripheral airway compression/closure results. This interferes with proper ventilation and may result in hypoxygenemia as a result of mismatch and trapping of airway contents such as mucus and germs, predisposing to infections[10,32–34]. Hypoxia caused by lung impairments, as discussed in the following section, may exacerbate adipose tissue dysfunction[2]. Finally, other obesity-related lung diseases, including COPD, asthma, hypoventilation syndrome, obstructive sleep apnea, and obesity and gastroesophageal reflux disease , may further predispose to infections [26,35].

Adiposopathy, chronic low-grade inflammation, and immune system dysfunction

Excessive fat accumulation, AT malfunction (distinguished by low-grade inflammation), and ectopic fat deposition, particularly visceral, all play important roles in the pathophysiology of obesity and its comorbidities [36–40]. Adipocyte hypertrophy is characteristic of dysfunctional AT, which itself is linked to persistent low-grade inflammation. AT inflammation is partially caused by adipocytes which are secreting pro-inflammatory cytokines [including tumour necrosis factor alpha (TNF-α), and monocyte chemoattractant protein-1, and various interleukins (IL) notably IL-1β, -6],

proinflammatory adipokines (leptin and resistin), and decreased levels of anti-inflammatory adipokines such as adiponectin, but also by the influx of numerous types of specialised, pro-inflammatory immune cells, such as macrophages[2,35,41,42]. Obesity may also have an imbalance in the pro- and anti-inflammatory immune cell ratio, favoring pro-inflammatory immune cell infiltration or activation and thus favoring an inflammatory state[2,16]. Moreover, adiposopathy is characterized by adipocytokine dysregulation, hormonal (insulin, catecholamines) resistance, impaired metabolism, reactive oxygen species (ROS)-induced stress and mitochondrial dysfunction, and anomalous oxygen levels, all of which pertain to ectopic fat accumulation and associated comorbidities[2,38,43,44]. Notably, in the presence of comorbidities such as OSA with hypoxic episodes of severe oxygen deprivation and acute duration, they may act negatively on the dysfunctional adipose tissue, leading to a vicious circle, as many adipocytokines appear to be oxygen-dependent, particularly in individuals with obesity[2,16]. As a result of these events, there is systemic inflammation, which may eventually compromise innate and adaptive immune function[35,45]. Confounding factors that could potentially affect immune response and infection risk independently of BMI could be comorbidities (cardiovascular disease, type 2 diabetes mellitus), altered nutrition (specific low-quality diets), and physical inactivity[9].

Increased TNF-, IL-1, and IL-6 Levels in adipocytokine dysregulation may result in a weakened immune response[17,45,46]. Additionally, increased circulating leptin levels (a hallmark of obesity, directly proportional to AT mass) could contribute to altered immune responses as many cell types of the innate immune system express leptin receptors[17,47,48]. For instance, monocytes appear to exert a more pronounced pro-inflammatory response, and neutrophils are even more reactive to ROS once they are treated with leptin *in vitro*[17,49,50]. Leptin appears to affect various stages of B and T cell maturation and functions[17,51,52]. Moreover, hyperleptinemia was shown to impact the host defense in humans and murine models *via* effects on neutrophils[17,53]. Metabolic dysfunction associated with hyperinsulinemia may also contribute to immune system dysregulation[17]. It is crucial to highlight that these mechanisms are not necessarily

exclusive and that they most likely interact to increase the overall incidence of lung infections in individuals with obesity. Furthermore, the mechanisms may differ based on the individual's underlying health problems and the kind of infection, as will be highlighted in the following sections.

COMMON INFECTIONS AND ONGOING CHALLENGSES

Obesity is associated with an increased risk of several respiratory infections, including tuberculosis, influenza, pneumococcal, staphylococcal, and more recently COVID-19-associated pneumonia[6,35,54]. Obesity and coexisting diabetes raise morbidity from pneumococcal pneumonia and influenza, and notably, diabetes influences TB control and increases drug resistance as well as mortality[35,55].

Bacterial infections

As the innate immune response, which is the first line of defense against pathogenic bacteria, is likely suppressed because of the persistent low-grade inflammatory status[26], obesity has been shown to have an impact on the outcome of severe bacterial infections[56]. Obesity appears to influence and increase the risk of Streptococcus pneumoniae in a variety of populations, particularly the elderly[57]. It has also been proposed that hyperleptinemia, which is commonly associated with obesity, affects host defense against S. pneumoniae in humans[58]. Obesity is associated with unfavorable clinical outcomes in adults with community-acquired pneumonia of various etiologies[59]. Moreover, a link between BMI and mortality in hospitalized patients with community-acquired pneumonia has been recorded[60]. Finally, diet-induced models of obesity have shown that excess adiposity affects the *in vivo* host defense against *Klebsiella pneumonia*[61].

Viruses of emerging interest

Obesity has been linked to an increased risk of several viral respiratory infections, including the notably recurrent influenza and ongoing COVID-19 pandemics, but also Respiratory Syncytial Virus (RSV) infection in children[6, 62–64].

When it comes to influenza, especially influenza A/pdmH1N1 viral infections, obesity appears to negatively impact humoral immunity[65] and the combined innate and adaptive responses already at the respiratory epithelium level[66–68]. Adiposity may also have a negative impact on influenza virus-related critical illnesses[69]. Immunomodulatory approaches to T cell metabolism have been explored to improve host immunity against influenza-related infections[70].

The potential negative impacts of obesity on COVID-19 have been largely described already[71,72]. Several studies have shown a direct link between obesity and COVID-19's severity and mortality[73,74]. Among other cardiometabolic risk factors, obesity appears to be a significant independent factor[75]. This appears to be the case for unfavorable outcomes in critically ill patients with COVID-19[76].

The COVID-19-associated pathophysiological response is associated with the expression of the angiotensin converting enzyme 2 (ACE2) receptors in target tissues[5,77-79]. Many organ systems, including the lungs, adipose tissue, and blood vessels, express ACE2 receptors[80]. Notably, higher levels of ACE2 have been hypothesized and demonstrated in the adipose tissue of individuals with obesity, suggesting that adipose tissue may play a role in acting as a "reservoir" for SARS-CoV-2[81,82]. The structural spike (S) protein of SARS-CoV-2 is responsible for significant immune response induction in the host and, *via* binding to ACE2 receptors on the target cells, mediates cellular invasion[83]. Likely to influenza viral infections, the role of hyperleptinemia in obesity has been speculated for COVID-19[84]. Finally, obesity-related low-grade chronic inflammation may be directly related to higher expression of ACE2 and pathway-associated components, as well as decreased vitamin D bioavailability, and gut microbiome dysbiosis [85-87].

Vaccinations in individuals with obesity

As demonstrated, obesity has a negative impact on the immune system, and these implications raise concerns about the absence of vaccine-induced immunity in these patients, necessitating a consideration of how this subpopulation might be better

protected[88,89].Cohort studies have shown that, particularly for influenza vaccination, individuals with obesity may have a lower immune response than those of normal weight[90,91]. Several degrees of evidence also suggest the importance of vaccination against COVID-19 and obesity, also from real-world data[92]. However, overall, the vaccination of individuals with obesity is of paramount importance and should not be avoided, even if reduced responsiveness is suspected.

CONCLUSION

In conclusion, obesity is a major risk factor for several respiratory infections and their severity. Changes in lung function, adipose tissue accumulation and dysfunction, and immune system dysfunction all contribute to the higher risk. It is important for individuals with overweight or obesity to undertake preventive steps to maintain their weight. These include dietary and habitual patterns that can lead and maintain weight loss and if necessary, following failure of these steps to implement medicinal avenues [93-95]. Preventive measures to lower the risk of lung infections including face covering and meticulous vaccinations against respiratory pathogens and frequent medical evaluations. Furthermore, healthcare practitioners should be aware of the increased risk of lung infections in these individuals and act in preventive ways and escalate treatment measures if necessary.

83337_Auto_Edited.docx

ORIGINALITY REPORT

3%
SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	30 words — 1%
2	Andrej Belančić, Andrea Kresović, Marija Troskot Dijan. " peptide ‐ 1 receptor agonists in the era of ‐ 19: Friend or foe? ", Clinical Obesity, 2021 Crossref	18 words — 1%
3	ec.europa.eu Internet	14 words — 1%
4	linknovate.com Internet	14 words — 1%

EXCLUDE QUOTES	ON	EXCLUDE SOURCES	< 12 WORDS
EXCLUDE BIBLIOGRAPHY	ON	EXCLUDE MATCHES	< 12 WORDS