Pulmonary Physiology and Pathophysiology in Obesity

Obesity and lung inflammation

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Mancuso P. Obesity and lung inflammation. J Appl Physiol 108: 722–728, 2010. First published October 29, 2009; doi:10.1152/japplphysiol.00781.2009.—The prevalence of obesity has increased dramatically worldwide, predisposing individuals to an increased risk of morbidity and mortality due to cardiovascular disease and type 2 diabetes. Less recognized is the fact that obesity may play a significant role in the pathogenesis of pulmonary diseases through mechanisms that may involve proinflammatory mediators produced in adipose tissue that contribute to a low-grade state of systemic inflammation. In animal models, inflammatory responses in the lung have been shown to influence the production of the adipocytokines, leptin and adiponectin, cytokines, acute phase proteins, and other mediators produced by adipose tissue that may participate in immune responses of the lung. An increased adipose tissue mass may also influence susceptibility to pulmonary infections, enhance pulmonary inflammation associated with environmental exposures, and exacerbate airway obstruction in preexisting lung disease. An increased understanding of the mechanisms by which obesity influences pulmonary inflammation may facilitate the development of novel therapeutic interventions for the treatment of lung disease.

macrophage; pneumonia; chronic obstructive pulmonary disease

THE PREVALENCE OF OBESITY in adults and children in the US and other developed nations has risen to epidemic proportions. Based on current estimates, 32% of the adult population and 16% of children aged 2–19 yr in the US are “obese”, based on weight classification by body mass index (BMI) (63, 64). Obesity increases morbidity and mortality from many chronic health ailments, such as cardiovascular disease, type 2 diabetes, dyslipidemia, and fatty-liver disease (55). Much less appreciated is the fact that respiratory illnesses, such as obstructive sleep apnea, aspiration pneumonia, hypoventilation syndrome, pulmonary embolism, chronic bronchitis, and asthma are also linked to obesity. Obesity, abdominal obesity in particular, compromises lung mechanics by restricting lung volumes, reducing chest wall compliance, and attenuating respiratory muscle efficiency (55). Less is known regarding the influence of excess adipose tissue on inflammatory responses in the lung that may underlie pulmonary diseases frequently observed in the obese. This review will focus on the evidence that obesity plays a critical role in pulmonary inflammation and the mechanisms by which mediators produced in the setting of obesity may significantly alter inflammatory responses in the lung.

DIFFICULTIES IN LINKING THE EFFECTS OF OBESITY WITH IMMUNE RESPONSES IN THE LUNGS

It should be noted that the interpretation of studies that have evaluated pulmonary inflammation in the setting of obesity are complicated by comorbid disturbances. Obesity is a complex metabolic condition that influences many physiological systems, including immune function. Alterations in one of these physiological systems alone or in combination can dramatically influence the response of the lungs to inflammatory stimuli. This contributes to the difficulty in attributing increases in adipose tissue mass in the obese to changes in the immune response in the lungs in the setting of disease. For example, gastroesophageal reflux disease is a common comorbid condition associated with obesity in humans. Gastroesophageal reflux disease is also an important risk factor for aspiration pneumonia (44) and asthma (40). Other comorbidities, such as hypertension and dyslipidemia, may also contribute to pulmonary inflammation observed in obese asthmatic subjects (76). Therefore, it is likely that obesity and its comorbidities collectively alter the immune response in the lungs, increasing susceptibility to asthma and aspiration pneumonia.

Animal models of obesity can also be complicated by comorbid conditions, such as leptin deficiency (ob/ob mouse) and leptin receptor deficiency (db/db mouse). Ob/ob and db/db mice exhibit metabolic abnormalities often observed in obese humans, such as hyperglycemia, glucocorticoid excess, and insulin resistance, along with defective innate and adaptive immune responses (12, 30, 32–34, 51, 53). In addition, these
Obese animals possess anatomic abnormalities, such as reduced nasopharyngeal volume, a consequence of smaller craniofacial structures, and smaller airways and lungs (76, 95). These physiological and anatomic abnormalities associated with ob/ob and db/db mice complicate their use as models of obesity in pulmonary disease. While diet-induced obesity may provide a more relevant model of human obesity, the high saturated fat content of the animal chow used to produce excess adiposity may differentially regulate inflammatory responses, since saturated fatty acids are known to be ligands for Toll-like receptor-4 (15, 48). Therefore, investigators should carefully consider confounding factors associated with obesity and inflammatory responses in the lung when interpreting the results of studies that employ the use of obese human subjects and animal models.

**ADIPOSE TISSUE IS AN ABUNDANT SOURCE OF PROINFLAMMATORY MEDIATORS THAT CAN INFLUENCE PULMONARY INFLAMMATION**

Adipose tissue is composed of mature adipocytes, preadipocytes, mesenchymal cells, and stromal cells that include vascular endothelial cells, macrophages, and fibroblasts. As a storage depot, adipose tissue buffers the influx of dietary lipids by clearing the circulation of triacylglycerol (TAG) and inhibiting the release of free fatty acids. During the obese state, the adipocyte is overloaded with TAG, and its ability to store more lipid declines. As a consequence, circulating levels of TAG and free fatty acids increase, leading to ectopic storage of lipids in skeletal muscle, the pancreatic islets, and the liver (25). Since fatty acids are ligands for Toll-like receptor-4, the increase in circulating fatty acids may also contribute to systemic inflammation (74).

In addition to storing triglycerides, white adipose tissue also functions as an endocrine organ by elaborating adipocytokines (adipocyte-derived hormones that are structurally similar to cytokines), cytokines, acute phase reactants, prostaglandins, and others that participate in local and distal physiological processes. The levels of adipocytokines influence glucose homeostasis and inform the host, via the central nervous system, regarding lipid energy storage. In the setting of obesity, the ability of the adipose tissue to elaborate adipocytokines, which possess proinflammatory properties, such as leptin, resistin, and visfatin, increases, and the synthesis of an anti-inflammatory adipocytokine, adiponectin, declines. The production of IL-6, TNF-α, acute phase reactants, C-reactive protein, serum amyloid A, complement fragment C3, and other immune modulating mediators also increase (86).

During the development of obesity, individual adipocytes undergo hypertrophy, and the vasculature fails to adequately perfuse the expansion of adipose tissue, resulting in tissue hypoxia and apoptotic cell death (13, 90). The cellular debris left behind from these cells induces the elaboration of chemokines, such as monocyte chemotactrant protein-1, which recruits macrophages and T cells from the peripheral circulation (43, 71). The recruited macrophages produce TNF-α, IL-6, and other cytokines, which inhibit adipocyte differentiation, preventing the maturation of preadipocytes that might be capable of buffering the increased influx of TAG. As a consequence, mature adipocytes continue to hypertrophy, become hypoxic, and undergo apoptosis, and the cycle of macrophage recruitment and cytokine production continues. The proinflammatory mediators produced in adipose tissue spill over into the peripheral circulation and contribute to a low-grade state of chronic systemic inflammation (73, 86).

Adipose tissue can respond to proinflammatory stimuli initiated in the lung via the systemic circulation to elaborate adipocytokines and other inflammatory mediators. Various inhaled stimuli in laboratory animals, such as bacteria, ozone (O_3), allergens, and particulate matter (PM), have been shown to activate adipose tissue via the systemic circulation to produce leptin, IL-6, and other immune modulating adipocytokines that may influence pulmonary inflammation (31, 36–39, 47, 51, 52, 84). Similarly, systemic administration of bacteria, IL-1β, LPS, and TNF-α have been shown to increase systemic adipocytokine levels (21, 26, 33). Based on these observations in animals, adipose tissue appears to function as an endocrine gland by releasing adipocytokines, cytokines, and other mediators that enhance local and systemic inflammatory responses.

**INCREASSE PERIPHERAL BLOOD LEUKOCYTES IN OBESITY**

Obesity-associated leukocytosis, a condition characterized by elevated peripheral blood white cell counts, has been reported by a number of investigators (28, 42, 60, 72, 93, 96). Womack et al. (93) observed that CD4^+ and CD8^+ T cells were elevated in obese woman compared with those having a normal BMI (<25 kg/m^2). Similarly, Kim and Park (42) reported that peripheral blood white cell counts were strongly correlated with subcutaneous obesity, and neutrophils were positively correlated with total adiposity and BMI. Other investigators have observed elevated levels of all leukocyte subsets (monocytes, neutrophils, and T lymphocytes) in obese children (96) and adults (28). In addition to studies on obese humans, elevated peripheral blood leukocyte counts have also been reported in some murine models of obesity, such as Cpefat/fat mice (38), but not in diet-induced obesity (37). Leptin and acute phase protein levels do not appear to be related to leukocytosis observed in obese animals (22) and humans (28), and the mechanisms responsible for elevated leukocyte counts in obesity are unknown. The enhanced systemic inflammation observed in the obese may be partially explained by increased peripheral blood leukocytes, which could potentially produce greater quantities of proinflammatory mediators systemically or after recruitment to the lung in the setting of disease.

**ROLE OF ADIPOCYTOKINES IN PULMONARY INFLAMMATION.**

Leptin was originally described as a satiety hormone produced by adipocytes that informed the host of peripheral lipid energy storage (98). The ability of leptin to influence the immune response, especially in the setting of obesity, has been the focus of numerous reports regarding its potential to enhance systemic and pulmonary inflammation (31, 36–38, 51, 75). The long (LepRb) and short isoforms (LepRa) of the leptin receptor are expressed by bronchial and alveolar epithelial cells and alveolar macrophages in the lung (3, 6, 10). Other cells of the immune system, such as monocytes, neutrophils, dendritic cells, mast cells, B and T lymphocytes, and natural killer cells, also express these receptors (46). Leptin has been shown to prime leukocytes for increased cytokine synthesis (24, 97),
enhanced reactive oxygen intermediate, and nitric oxide production (11, 70) in vitro.

Previous reports demonstrating that leptin upregulates leukotriene (LT) biosynthesis and enhances the expression of key regulatory enzymes in the LT biosynthetic pathway may provide a link between obesity and pulmonary inflammation in the setting of asthma (asthma and obesity are reviewed by Shore in this series of reviews) (41, 50–52, 54, 87). This notion is supported by the fact that therapeutic responses to the cysteinyl-LT receptor antagonist, montelukast, persisted with increasing BMI in adults with modest asthma (68). Although the capacity for enhanced LT synthesis in obese asthmatic subjects has not been demonstrated, it is noteworthy that increased activity of sPLA2, an enzyme known to liberate arachidonic acid for subsequent conversion to LTs, has been observed in obese patients with acute exacerbations of asthma (57). In total, the increased synthesis of leptin in the obese appears to promote proinflammatory responses systemically and in the lung by increasing cytokine and LT synthesis. While there is evidence that cells in the lung might be capable of producing leptin (9, 10), it most likely leaks in to the respiratory tract due to increases in microvascular permeability as a consequence of pulmonary inflammation (75). Despite the numerous publications on the pleotropic effects of leptin, there is much yet to be learned regarding its role in pulmonary inflammation.

In contrast with leptin, adiponectin is an adipocytokine whose synthesis declines with increased adiposity and during an inflammatory response (45). While little is known regarding the importance of adiponectin in pulmonary inflammation of obese human or animal subjects, there is some evidence that adiponectin plays a significant role in the pathogenesis of lung disease. All three of the known adiponectin receptors (AdipoR1, AdipoR2, and T-cadherin) are expressed in the lungs (78), and adiponectin has been isolated from bronchoalveolar lavage fluid (83). In addition, exogenously administered adiponectin was shown to suppress leukocyte recruitment, Th2 cytokine production, and airway inflammation in a murine model of allergen-induced asthma (78). Interestingly, the lungs of adiponectin-deficient mice exhibit an emphysema-like phenotype that is associated with activated alveolar macrophages that spontaneously elaborate TNF-α and matrix metalloproteinase-12 (83). This suggests that adiponectin deficiency may be associated with the pathogenesis of inflammatory lung diseases, such as emphysema. Another report indicating that adiponectin deficiency is associated with pulmonary inflammation and remodeling of the lung was recently published by Medoff et al. (56). In a model of allergen-induced chronic asthma, adiponectin-deficient mice exhibited increased pulmonary inflammation, severe pulmonary arterial muscularization, and pulmonary arterial hypertension (56). Thus reduced levels of adiponectin, the most abundant adipocytokine in peripheral blood (~10 μg/ml) (45), may be an important mechanistic link between obesity and pulmonary inflammation associated with asthma and vascular remodeling in pulmonary hypertension (56). Adiponectin, and its absence, seems to have a profound effect on the lung, and future experimental exploration of the effects of this adipocytokine in the pathophysiology of pulmonary disease in obese subjects is strongly encouraged.

Leptin and adiponectin have been the subjects of numerous investigations due to their being the most abundant adipocytokines found in serum and the commercial availability of transgenic animals and reagents. While our understanding of the roles of these adipocytokines in pulmonary disease is still taking shape, more research is needed to determine whether other adipocytokines (visfatin, resistin, retinol binding protein-4, vaspin, omentin, and many others) participate in inflammatory diseases of the lung.

**OBESITY AND LUNG INFLAMMATION DURING INFECTIOUS PNEUMONIA**

Obese humans, many of whom are type 2 diabetics, have a greater susceptibility to subcutaneous infections associated with poor wound healing (14) and intensive care unit-acquired catheter and bloodstream infections (16). Based on this information, one might expect to observe greater infectious pneumonia among the obese. In contrast, the low-grade chronic systemic inflammation associated with obesity could potentially enhance pulmonary immune responses against respiratory infections and, potentially, augment host defense of the lung. Whether or not obese subjects exhibit greater susceptibility to infectious pneumonia is controversial. Some have reported an increased risk for pulmonary nosocomial infections in obese patients (7, 61, 94), while others have not (8, 17, 58). Apart from one case study that reported overwhelming blastomycosis pneumonia in five obese patients (67) and a prospective study that demonstrated an association between a 40-lb weight gain and a twofold increased risk of community-acquired pneumonia (2), very little is known regarding the influence of obesity on community-acquired pneumonia. Since the number of overweight and obese is likely to increase for the foreseeable future, additional research is needed to determine whether the inflammatory response and susceptibility of this population to infections of the respiratory tract differ from that of normal-weight individuals.

There are a limited number of reports that have evaluated the effects of obesity on pulmonary inflammation during bacterial (31, 51), mycobacterial (65, 91), or viral (79, 80) pneumonia in animal models. In general, leptin-deficient (ob/ob) and leptin-receptor deficient (db/db) mice are more susceptible to bacterial infections and pneumonia (31, 33, 51, 53, 66). Compared with their lean wild-type (WT) counterparts, proinflammatory cytokine [TNF-α, IL-12, IL-6, and macrophage inflammatory protein-2 (MIP-2)] production was not different (51), reduced (92), or elevated (TNF-α, MIP-2, PGE2) (31) in ob/ob mice following an intrapulmonary challenge with bacteria. In the report by Hsu et al. (31), pulmonary bacterial loads and polymorphonuclear neutrophils recruited to the lungs were higher in ob/ob mice, which would have provided a more robust stimulus for inflammatory mediator production. Similarly, others have reported a more robust and persistent inflammatory response in ob/ob mice after a subcutaneous bacterial infection (59).

Wieland and colleagues observed lower levels of IFN-γ in ob/ob mice in murine tuberculosis, compared with lean WT animals, despite higher pulmonary M. tuberculosis loads (91). Similarly, a study by Ordaway and colleagues (65) reported that the influx of IFN-γ+ CD4+ T cells was delayed in ob/ob, compared with WT mice, following M. avium challenge. In these experiments, M. abscessus burdens were higher in ob/ob mice, and mycobacterial clearance was delayed. Since leptin or leptin receptor deficiency is known to suppress both innate and
adaptive immune responses, the alterations in pulmonary inflammation in ob/ob mice following mycobacterial infection cannot be attributed to obesity alone (31, 51, 52, 65, 91).

There is also evidence that obesity impairs adaptive immune responses against viral infection. For example, diet-induced obese mice exhibited increased mortality that was associated with impaired natural killer cell cytotoxicity, a delay in the production of IL-6 and TNF-α and minimal induction of IFN-α and -β, following infection with the influenza A virus (79). A subsequent study revealed that diet-induced obesity impaired the recruitment of mononuclear and CD8+ T cells to the lung, diminished dendritic cell antigen presentation, and attenuated IL-2 and IL-12 production (80). While there are no studies that have demonstrated that obese humans are more susceptible to respiratory viral infections, reduced antibody responses to vaccination have been observed in obese human subjects (20, 89). These observations suggest that obesity may impair pulmonary host defense against viral infection and attenuate adaptive immune responses in the lungs. In light of the potential for pandemic influenza and the increasing population of overweight and obese, further exploration of the influence of obesity on the host response to respiratory viral infections is encouraged.

**SUSCEPTIBILITY OF THE OBSESE TO PULMONARY INFLAMMATION INDUCED BY O₃ OR PM**

The obese may be uniquely vulnerable to lung inflammation induced by O₃, since obese humans and animals exhibit enhanced pulmonary inflammatory responses following exposure (37, 38, 77). O₃ exposure is a relevant environmental pollutant known to enhance pulmonary inflammation by increasing the secretion of proinflammatory cytokines and leukocyte recruitment to the lungs and inducing the leakage of plasma fluid into the alveolar space by disrupting the integrity of the alveolar epithelium (29). These responses may be enhanced in obese human subjects, since O₃ exposure induces a greater decline in lung function in the obese compared with nonobese human subjects (1, 4). Following O₃ exposure, bronchoalveolar lavage fluid protein, IL-6, the chemotactants, KC, MIP-2, monocyte chemoattractant protein-1, and neutrophils were increased in obese Cpbagfubf mice compared with their lean WT counterparts (38). Similarly, bronchoalveolar lavage fluid protein, IL-6, KC, MIP-2, IP-10, and eotaxin were increased in diet-induced obese compared with lean mice (37).

Serum leptin levels are increased in obese humans with asthma, and leptin has been shown to exacerbate O₃-induced lung inflammation (36, 49, 88). However, not all studies have reported this association (35, 81, 85). Augmented pulmonary inflammatory responses to O₃ have been observed in both ob/ob and db/db mice (49, 77). In ob/ob mice (47), the increased bronchoalveolar lavage protein, IL-6, and neutrophils following O₃ exposure could be attenuated with a neutralizing antibody against IL-6. Based on these reports, it appears that the enhanced inflammation in lungs of the obese following O₃ exposure is not leptin dependent. However, leptin can exacerbate pulmonary inflammation in response to O₃, but other factors, such as IL-6, may be responsible for this enhancement (77).

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**Fig. 1. Overview of the influence of obesity on inflammation in the lung.** Adipose tissue expands with positive energy balance, resulting in increased adipocyte hypertrophy. As the individual adipocytes grow larger, they become hypoxic due to the failure of the vascular system to adequately perfuse the enlarged adipose tissue. As individual adipocytes undergo apoptosis, chemokines such as monocyte chemoattractant protein-1 (MCP-1) are produced, and macrophages are recruited to adipose tissue to remove remaining cellular debris. During this process, a cycle of macrophage recruitment and activation occurs, resulting in the increased production of TNF-α and IL-6. In addition, the expanding adipose tissue increases the production of proinflammatory adipokines (leptin, resistin, visfatin) and reduces adiponectin (an anti-inflammatory mediator) synthesis. An increased production of acute phase reactants, triacylglycerol (TAG), and free fatty acids (FFA) also spill over into the peripheral blood. Increased numbers of peripheral white blood cells (WBC) have also been observed in the obese. When the respiratory system is challenged by ozone (O₃), particulate matter (PM), allergens, or bacteria, cytokines generated in the lungs (TNF-α, IL-1β, and IL-6), and LPS from disseminated bacteria can enhance the production of proinflammatory mediators released systemically by adipose tissue. The augmentation of systemic inflammation in the obese can enhance pulmonary inflammatory responses by enhancing leukocyte recruitment, cytokine production, microvascular permeability, and edema, which could potentially increase airway obstruction in preexisting lung disease.
The obese may also be more susceptible to PM-induced pulmonary inflammatory responses, although limited evidence supports this hypothesis. Alterations in pulmonary mechanics, such as an increased respiratory rate to compensate for reduced tidal volume, may increase the deposition of PM in the lungs of the obese. In a study by Bennett and Zeman (5), BMI was associated with graded increases in the estimated total lung dose of fine particulates in an inhalation study involving healthy 6- to 13-year-old children. In addition, an enhanced systemic inflammatory response, as indicated by serum C-reactive protein levels averaged over 1–7 days, was greater in the obese following exposure to ambient fine PM (18). Given the potential for aggravated pulmonary inflammatory responses in the obese following exposures to PM and other types of air pollution, additional studies are warranted.

CHRONIC BRONCHITIS AND OBESITY

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality globally and is increasingly associated with obesity (23). While the prevalence of obesity is more common in COPD than in the general population, overweight and obesity are most often associated with chronic bronchitis rather than emphysema (19, 27). Obesity modifies the clinical course of COPD by increasing the muscular effort required for ventilation with greater dyspnea and ultimately reduced exercise tolerance (23). As a consequence, sedentary behavior in patients with chronic bronchitis leads to greater fat accumulation and, potentially, further airway obstruction. While weight loss has been shown to reduce airway obstruction in asthmatic subjects (82) and improve symptoms associated with obstructive sleep apnea in the obese (62), changes in lung function associated with weight loss in chronic bronchitis have not been reported (69).

Airway obstruction in chronic bronchitis is caused by mucus hypersecretion and bronchial wall thickening, which contribute to narrowing of the airway lumen. While there are no studies that have evaluated the impact of obesity on airway obstruction or inflammation in chronic bronchitis, the low-grade systemic inflammation and increased peripheral blood leukocyte counts observed in the obese could potentially worsen chronic airway obstruction and acute exacerbations. Given the increased prevalence of obesity in patients with chronic bronchitis (27), the evaluation of the impact of obesity on the mechanisms of airway obstruction and inflammation are strongly encouraged.

CONCLUSIONS

Significant progress has been made toward the understanding of the biology of adipose tissue through the study of adipocytokines and how they may link obesity with the immune system and chronic inflammatory diseases. Studies conducted in laboratory animals have demonstrated that inflammatory responses initiated in the lung can induce the production of leptin, IL-6, and other proinflammatory mediators from adipose tissue. In addition, a role for adiponectin as an inhibitor of acute phase reactants, and lipids elaborated by adipose tissue. In addition, a role for adiponectin as an inhibitor of leptin, IL-6, and other proinflammatory mediators from adipose tissue through the study of active protein levels averaged over 1–7 days, was greater in the obese following exposure to ambient fine PM (18). Given the potential for aggravated pulmonary inflammatory responses in the obese following exposures to PM and other types of air pollution, additional studies are warranted.

REFERENCES

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