Published in final edited form as:
Pulm Pharmacol Ther. 2013 August ; 26(4): 412–419. doi:10.1016/j.pupt.2012.04.006.

Obesity and respiratory infections: Does excess adiposity weigh down host defense?

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Abstract

The number of overweight and obese individuals has dramatically increased in the US and other developed nations during the past 30 years. While type II diabetes and cardiovascular disease are well recognized co-morbid conditions associated with obesity, recent reports have demonstrated a greater severity of illness in obese patients due to influenza during the 2009 H1N1 pandemic. Consistent with these reports, diet-induced obesity has been shown to impair anti-viral host defense in murine models of influenza infection. However, the impact of obesity on the risk of community-acquired and nosocomial pneumonia in human patients is not clear. Relatively few studies have evaluated the influence of diet-induced obesity in murine models of bacterial infections of the respiratory tract. Obese leptin deficient humans and leptin and leptin-receptor deficient mice exhibit greater susceptibility to respiratory infections suggesting a requirement for leptin in the pulmonary innate and adaptive immune response to infection. In contrast to these studies, we have observed that obese leptin receptor signaling mutant mice are resistant to pneumococcal pneumonia highlighting the complex interaction between leptin receptor signaling and immune function. Given the increased prevalence of obesity and poor responsiveness of obese individuals to vaccination against influenza, the development of novel immunization strategies for this population is warranted. Additional clinical and animal studies are needed to clarify the relationship between increased adiposity and susceptibility to community-acquired and nosocomial pneumonia.

Introduction

The prevalence of obesity among adults living in the US has increased to alarming levels with 34% obese (BMI≥30) and 68% overweight (BMI=25-29.9) [1]. Moreover, 46-54% of hospitalized patients are overweight, 32% are obese, and 5% are extremely obese with a BMI (BMI≥40) [2]. Similar trends have been observed in other developed nations raising global concerns about the chronic health consequences of obesity [3]. While type II diabetes, cardiovascular disease, and non-alcoholic fatty liver disease are well known co-morbid conditions associated with obesity, the evidence that excess white adipose tissue suppresses pulmonary host defense against infection is emerging [4-7]. The recent observation that the obese were uniquely susceptible to and suffered more severe outcomes from the 2009 H1N1

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influenza pandemic underscores the need to elucidate the effects of obesity on innate and adaptive immune responses against respiratory infections [8]. This review will examine the evidence that obesity contributes to a greater severity of respiratory infections in humans and in animal models and will also discuss potential mechanisms underlying these responses.

I. Co-morbid conditions associated with obesity compromise pulmonary host defense

Obesity is a complex condition that is characterized by excess white adipose tissue and is often accompanied by other co-morbid conditions, such as gastroesophageal reflux disease (GERD) and type II diabetes, known to compromise host defense against infection [9]. Both GERD and type II diabetes, even in the absence of excess adiposity, have been shown to compromise host defense by impairing innate and adaptive immunity [10-11].

Obesity and gastroesophageal reflux disease (GERD)

Obesity is associated with larger gastric volumes and the accumulation of visceral adipose tissue known to increase gastric pressure. The combination of these factors compromise lower esophageal sphincter closure. As a consequence, reflux of gastric fluid occurs and this fluid can be aspirated into the respiratory tract resulting in pneumonia [12]. GERD is common in patients with abdominal obesity who are at a greater risk for aspiration pneumonia [10]. Positioning these patients in a semi-upright position during sleep and hospitalization can decrease symptoms associated with GERD and aspiration pneumonia [13-14]. It is also important to note that GERD is very common among those recovering from bariatric surgery and these patients should be monitored for reflux to prevent aspiration pneumonia [15-16].

Host defense and diabetes

Type II diabetes is fairly common among those who are overweight or obese and this condition is a well established risk factor for infectious disease for many reasons [17]. Diabetes is known to delay wound healing, impair host defense against skin and cutaneous infections, and is associated with nosocomial infections and infectious complications of surgery [17]. Interestingly, a recent study by O'Brien et al. demonstrated impaired wound healing in obese hyperglycemic mice after infection with the influenza virus [18]. It is also an important risk factor for pneumonia and influenza [11] and contributes to a higher risk of death from community-acquired pneumonia [19].

Adipose tissue inflammation, nutrient excess, and immune suppression

The accumulation of adipose tissue during obesity may attenuate pulmonary host defense through metabolic disturbances that often accompany this condition. Adipose plays an important role in storing excess calories in the form of triacylglycerol (TAG). In addition to serving as a buffer for dietary TAG, adipose tissue is an endocrine gland. As this tissue expands, its ability to buffer dietary lipids declines resulting in elevated blood TAG and free fatty acids (FFA). As a consequence, these lipids increase in the peripheral circulation and accumulate in ectopic sites such as skeletal muscle, the liver, and islets of the pancreas which leads to insulin resistance and hyperglycemia [20]. In addition, adipose tissue elaborates proinflammatory cytokines (TNF-α, IL-6, IL-1β, IL-18, MCP-1), proinflammatory adipokines such as leptin and resistin, and produces less anti-inflammatory adipokines such as adiponectin. The consequence of these events is systemic inflammation which may ultimately impair innate and adaptive immune function by inducing endoplasmic reticulum stress, lipotoxicity, oxidative stress, and leptin resistance [21-22]. (Summarized in Figure 1).

II. Obesity is a risk factor for the severity of illness from influenza

The H1N1 influenza pandemic of 2009 provides the strongest evidence that the obese exhibit greater susceptibility to pulmonary viral infections [5, 23]. A number of reports indicated that the obese and morbidly obese appeared to be more susceptible to and exhibited a greater severity of illness from the H1N1 influenza pandemic of 2009[5, 23-25]. Additional studies confirmed these associations indicating that obesity and morbid obesity were independent risk factors for hospitalization [26], admission to an intensive care unit [27], and critical illness and death [23, 28] associated with H1N1 infection in the US[29]. Similar reports from many other countries also indicate a greater severity of illness and death from pandemic H1N1 in obese patients [30-35] (Summarized in Table 1). While this information suggests that obese individuals should receive annual seasonal influenza vaccinations, obesity is associated with a greater decline in influenza vaccine antibody titers and defective influenza-specific CD8+T cell function [36]. A novel influenza vaccine strategy may be required to protect obese humans from seasonal influenza. Finally, since mortality from influenza is often associated with secondary bacterial pneumonia, future studies should investigate potential associations between obesity and the possibility that these individuals may be more likely to develop secondary bacterial pneumonia.

III. Diet induced obese mice exhibit increased mortality and impaired host defense against influenza-infection

Diet Induced Obese (DIO) mice and influenza A infection

The recent obesity epidemic is most likely due to a positive energy balance that commonly occurs as a consequence of an energy rich diet and limited physical activity. Many investigators have taken a similar approach in producing DIO mice by feeding these animals diets consisting of 40-60% fat, usually in the form of saturated fatty acids, to induce obesity within a relatively short period of time (100-120 days) [37]. Using the DIO model, a number of studies that have examined the effects of obesity on mechanisms of host defense against influenza infection [18, 21, 38-40]. In the first study to demonstrate that obesity increases the risk of death from influenza infection, Smith et al. observed that DIO mice exhibited greater mortality, increased lung pathology scores, and a defective cytokine response following infection with a mouse adapted influenza virus (Influenza A/PR8/34) [38]. The impairment in host defense in DIO mice was associated with a decrease in type I IFNs (IFN-α and IFN-β), a delay in the expression of IL-6 and TNF-α that eventually increased to levels greater than that observed in lean animals, and impaired natural killer (NK) cell cytotoxicity. Subsequent studies revealed that DIO also impairs the ability of dendritic cells to present antigens to T cells, attenuating monocyte and CD8+T cell recruitment, and diminishing IL-2 and IL-12 production following influenza infection [39]. Following a primary challenge with non-lethal influenza H3N2, Karlsson et al. demonstrated that DIO mice exhibited increased morbidity and mortality following a secondary infection with influenza A/PR/8 that was associated with reduced CD8+ T cell, IFN-γ production, and defective antigen presentation by dendritic cells [21, 41]. This impairment was due to an inability of DIO mice to generate and maintain functional antigen specific memory CD8+ T cells.

DIO mice and pandemic H1N1 infection

Recent studies by Easterbook et al. and O'Brien et al. showed that DIO mice experience greater mortality despite similar viral loads following infection with the 2009 pandemic H1N1 influenza virus [40, 42]. In the report by Easterbrook, the authors observed that pulmonary IFN-β and proinflammatory cytokine production in DIO mice were lower than in lean control animals. Interestingly, serum cytokine levels were elevated in DIO and this response did not occur after influenza infection in lean mice. In a study by O'Brien et al.,

increased mortality in DIO and *ob/ob* mice following H1N1 infection was associated with increased lung pathology, impaired wound repair and subsequent pulmonary edema [42]. The results of these studies are summarized in Figure 2, a picture adapted and updated from a review published by Karlsson et al. [41]. While these reports provide valuable insights into mechanisms by which obesity may impair host defense against influenza infection, future studies should examine the direct effects of nutrient excess (i.e. elevated blood lipids and hyperglycemia), endoplasmic reticulum and oxidative stress, and leptin resistance on intracellular signaling pathways and effector functions in NK cells, macrophages, CD4+ T cells, effector CD8+T cells, plasma B cells, DCs, and other cells known to participate in the anti-viral response [21]. The use of cells recovered from obese patients and mice that become obese due to hyperphagia, a more physiologically relevant model, rather than a high fat diet, are also encouraged.

IV. Does obesity increase the risk of community-acquired or nosocomial pneumonia?

Obesity and risk of community-acquired pneumonia

While there is ample evidence that shows an increased risk of bacterial infections of the feet, surgical and catheter sites, gingival and periodontal tissues, gastrointestinal tract, and of the skin in obese patients, the impact of obesity on bacterial pneumonia is less certain [14]. Community-acquired pneumonia is most frequently caused by bacterial pathogens. Paradoxically, three studies have demonstrated a protective association between obesity and mortality from pneumonia [43-45]. Corrales-Medina et al. [43] demonstrated that increasing BMI was negatively correlated with 30-day mortality in patients with proven pneumococcal or *Haemophilus* community-acquired pneumonia. Similarly, LaCroix et al. [44] reported a negative relationship between mortality from pneumonia and BMI with increased mortality in men in the lowest BMI quartile compared with the highest BMI quartile. This study also suggests that the obese were protected from pneumonia as a cause of death. In a study that evaluated protective factors against death from pneumonia in 110,000 Japanese subjects, Inoue et al. [45] reported that low BMI (<18) was associated with an increased risk of death while the opposite was true for subjects with a high BMI (25-30.9). The reported associations between lower BMI and an increased risk of death from pneumonia [43-45] probably reflects the greater frequency of chronic diseases associated with malnutrition, e.g. emphysema, known to increase one's susceptibility to pneumonia. In contrast to these, a study by Baik et al., which included 26,429 men aged 44 to 79 years from the Health Professionals Follow-up Study and 78,062 women aged 27 to 44 years from the Nurses' Health Study II, demonstrated a significant association between a 40-lb weight gain and a twofold increased risk of community-acquired pneumonia [46]. Only one study, at the time that this review was written, has demonstrated an association between childhood obesity and respiratory infections [47]. In this study, the authors reported that overweight and obese children (BMI in the 90th percentile) experienced twice as high a risk for acute respiratory infections (the cause of which was not identified) than children with a low BMI. At present, the effect of obesity on susceptibility to community-acquired bacterial pneumonia is uncertain. However, the disparity in these reports may be due to the endpoints reported. For example, obesity was associated with a lower risk of mortality from community-acquired pneumonia in the studies by Corrales-Medina, LaCroix, and Innoe [43-45] and a higher risk of respiratory infection in the studies by Baik and Jedrychowski [46-47]. Based on these reports, it is possible that obesity increases susceptibility to community-acquired pneumonia while reducing the risk of mortality. However, additional research is needed to reach an appropriate conclusion.

Obesity and risk of nosocomial pneumonia

Obese patients experience more complications while hospitalized for critical illness and after surgery requiring greater hospital and ICU lengths of stay. Although there are numerous studies demonstrating that obesity is associated with a greater risk of surgical site infections [48], wound infections, catheter and blood stream infections [49], and infections of the urinary tract [50], the data on the association between obesity and the risk of nosocomial pneumonia, which is most often caused by bacteria, are mixed. For example, a prospective study by Bochicchio et al. involving 1167 critically ill trauma patients demonstrated that obesity was associated with increased hospital and ICU lengths of stay and a twofold increased risk of urinary tract and blood stream infections, and pneumonia [4]. Similarly, Newell et al. also observed an increase in hospital and ICU lengths of stay, increased urinary tract infections, a longer period of ventilator support, as well as an increased risk of pneumonia in obese and severely obese critically injured blunt trauma patients [6]. A retrospective chart review of patients admitted to medical ICUs conducted by Yaegashi et al. [7] revealed that morbidly obese patients, defined as BMI ≥40, had higher rates of mortality, acute respiratory distress syndrome, catheter infections, acute renal failure, nosocomial pneumonia, and sepsis than obese patients with a BMI in the range of 30-39.9. The morbidly obese also required a longer period of time on ventilatory support. Finally, in a retrospective study which included patients admitted to a Level 1 trauma center, Serrano et al. observed an increased risk of nosocomial pneumonia among obese patients [51]. In contrast to the studies mentioned above, studies by Brant et al. [52] and Moulton [53] did not find a significant association between obesity and an increased risk of nosocomial pneumonia in patients undergoing heart surgery. In agreement with Brandt and Moulton, Dossett et al. did not find a significant association of BMI with pulmonary complications (such as pneumonia) in a cohort study of critically injured adults [54]. The lack of agreement of these studies may be due to the reason for admission. For example, the increased risk of pneumonia may be observed among obese trauma patients rather than those who have had surgery. In total, based on available evidence, an association between obesity and community-acquired or nosocomial pneumonia is not clear and additional research is needed. In the future, investigators should identify the cause of infectious pneumonia since it is likely that obesity selectively impairs the immune response to some but not all infectious agents. Table 2 provides a summary of some of the studies mentioned above.

V. Effect of leptin and leptin receptor deficiency on susceptibility to infection in mice and humans

Leptin and leptin receptor deficiency impairs host defense against pulmonary bacterial infections

Most investigators have used leptin (*ob/ob*) and leptin receptor (*db/db*) deficient mice which are not only obese but exhibit many immune and endocrine abnormalities that are caused by both leptin deficiency and obesity which complicates the interpretation of these studies [42, 55-58]. Leptin is essential for normal development and function of cells of the myeloid and lymphoid linage affecting both innate and adaptive immune responses and the absence of this hormone or its receptor results in severe immune abnormalities and greater susceptibility to viral [42, 59], bacterial [55-56], mycobacterial [57-58], and fungal infections[60]. In general, leptin promotes T_H1 cytokine production and the elaboration of proinflammatory lipid mediators [61-63]. It's also been shown to promote immune cell survival [64]. Studies conducted in our laboratory have shown that *ob/ob* mice exhibit increased pulmonary bacterial burdens and reduced survival following an intratracheal challenge with either *K. pneumoniae* or *S. pneumoniae* [55-56]. In comparison with WT animals, *ob/ob* mice produced proinflammatory mediators (TNF-α, IL-6, IL-12, and MIP-2) that were not different [55], reduced [57, 65], or elevated (MIP-2, PGE_2, TNF-α) [56] following intrapulmonary bacterial

challenge. In a study conducted in by Hsu et al., neutrophil (PMN) recruitment to the lung in response to *S. pneumoniae* challenge was enhanced in *ob/ob* mice. The host defense impairment in these animals was related to defective alveolar macrophage and PMN phagocytosis and killing of bacteria in vitro [56]. These defects suggest an essential role for this adipokine in leukocyte antibacterial effector functions. Leptin is known to induce actin polymerization [66], upregulate complement receptor (CD11b/CD18) expression in monocytes [67] and PMNs [68], and enhance the production of reactive oxygen intermediates by inducing the assembly of the NADPH oxidase complex [69-70]. Leptin deficiency is also associated with reduced leukotriene synthesis which is known to contribute to impaired pulmonary host defense against bacterial pneumonia [55, 63, 71-73]. Interestingly, the provision of exogenous leptin restored host defense and leukotriene synthesis in states of leptin deficiency [55, 71]. The ability of leptin to enhance macrophage leukotriene synthesis has also been demonstrated in cells from wild type animals and this might be an additional mechanism by which it promotes host defense in the lung [63, 74-75].

In regard to mycobacterial infections, Wieland et al. reported higher lung *M. tuberculosis* counts in *ob/ob* compared with WT mice that was associated with reduced levels of IFN-γ in a murine model of tuberculosis [58]. Ordway reported similar results in that IFN-γ+ CD4+ T cell recruitment to the lungs was delayed in *ob/ob,* compared with WT mice challenged with *M. abcessus* [57]. Lung *M. abcessus* burdens were higher and mycobacterial clearance was delayed in *ob/ob* mice. Similarly, *Ob/ob* and *db/db* mice also exhibit impaired host defense against many other bacterial, fungal, and viral infections of the CNS, liver, paw, stomach, heart, gut, and peritoneum[59, 76-81]. While human leptin deficiency is rare, individuals with this genetic defect are known to exhibit greater susceptibility to respiratory infections indicating an important role for leptin in the human immune response to infectious disease as well [82]. Despite these advances in pulmonary host defense and leptin deficiency, further evaluation of the mechanisms by which this adipokine regulates innate and adaptive immunity is warranted.

Effects of leptin receptor signaling and leptin resistance in infection

While there is disagreement in the literature regarding the susceptibility of the obese to community-acquired and nosocomial pneumonia, obesity appears to be a risk factor for influenza and possibly other viral infections. As mentioned above, obesity is associated with a chronic state of systemic inflammation and one might infer that this condition would lead to a heightened state of host defense. However, there is more agreement that obesity impairs host defense against influenza infection and this may occur via leptin resistance and metabolic dysfunction. Leptin resistance is a condition by which cells become insensitive to leptin as a consequence of prolonged exposure to elevated levels of this adipokine [83]. This effect is mediated through the down regulation of LepRb in immune cells and the prolonged activation of STAT3 signaling resulting in the accumulation of intracellular SOCS3 which inhibits further leptin receptor signaling[84]. Leptin resistance has been demonstrated in NK cells [85], T cells [86], and peripheral blood monocytes [87] and this might contribute to suboptimal responses in the obese during influenza infection. Lastly, it is interesting to note that polymorphisms in the human leptin receptor gene have not only been associated with obesity but with susceptibility to infectious disease as well [88-89]. It is envisioned that leptin receptor mutations in humans may be related to impairments in pulmonary host defense that may or may not be associated with an obese phenotype. Alternatively, leptin receptor mutations can lead to obesity and a protective immune phenotype against pulmonary infections [75]. In total, more research is needed to determine the role of leptin receptor dysfunction in infectious disease.

VI. Role of adiponectin and other adipokines in pulmonary infections

Besides leptin, very little is known regarding the importance of other adipokines in host defense against infection. Adiponectin, an adipokine with anti-inflammatory properties, has been shown to play a role in alveolar macrophage activation and the lungs of knockout mice exhibit an emphysematous phenotype [90]. Exogenous administration of adiponectin has been shown to suppress leukocyte recruitment and it plays an anti-inflammatory role in allergic airway disease in murine models [91-92]. Adiponectin levels are reduced in obese subjects and its role in infectious disease is unknown [93]. Blood adiponectin levels are elevated in human patients with *M. avium-intracellulare* complex pulmonary infection [94] and in mice following influenza infection [95]. Interestingly, Uji et al. observed that adiponectin-knockout mice exhibit greater mortality in a murine model of polymicrobial sepsis and that pharmacologically induced increases in serum adiponectin improved survival[96]. Adiponectin also facilitates the uptake of apoptotic cells [97] by macrophages and this response is critical for reducing inflammation in the lungs [98-99]. Additional studies that evaluate the role of adiponectin in pulmonary host defense against infection are warranted since the levels of this adipokine are reduced in obese humans [100].

In regard to other adipokines and host defense against respiratory infections, lipocalin 2, which is produced in abundance by adipose tissue of obese mice and humans, has been shown to play a protective role against Klebsiella and *E.coli* pneumonia [101-102]. As discussed above, it is uncertain whether or not the obese are more susceptible to bacterial pneumonia. Evaluating a potential association between elevated serum lipocalin 2 levels and respiratory infections in obese human subjects may provide more insight into physiologic role of adipokines and host defense. Finally, nothing is known regarding the role of resistin, retinoic acid binding protein 4, and other proinflammatory adipokines produced in abundance in the obese during infections of the respiratory tract.

Conclusions

Health care professionals are well acquainted with the association between obesity, type II diabetes, athlerosclerosis, and ischemic heart disease. However, overweight and obese adults and children may also be especially susceptible to respiratory infections and this was evident during the recent H1N1 influenza pandemic of 2009. Since the prevalence of obesity is likely to be stable within the foreseeable future, this condition should be recognized as a chronic medical condition known to increase the risk of influenza-related complications requiring vaccination against seasonal influenza. Only a small number of studies have characterized the mechanisms by which obesity increases the risk of influenza in animal models and this research should be expanded to increase our understanding of the mechanistic underpinnings of this association. Even less is known regarding the susceptibility of the obese to bacteria and other respiratory pathogens and this warrants further investigation. Finally, future studies should also determine if therapeutic strategies employed to prevent obesity-related metabolic and cardiovascular disease, such as weight loss, would also improve immune function against respiratory infections.

Acknowledgments

Support for the author was provided by a grant from the National Institutes of Health, HL077417, and a Clinical Innovator Award (CIA-103071) from the Flight Attendants Medical Research Institute.

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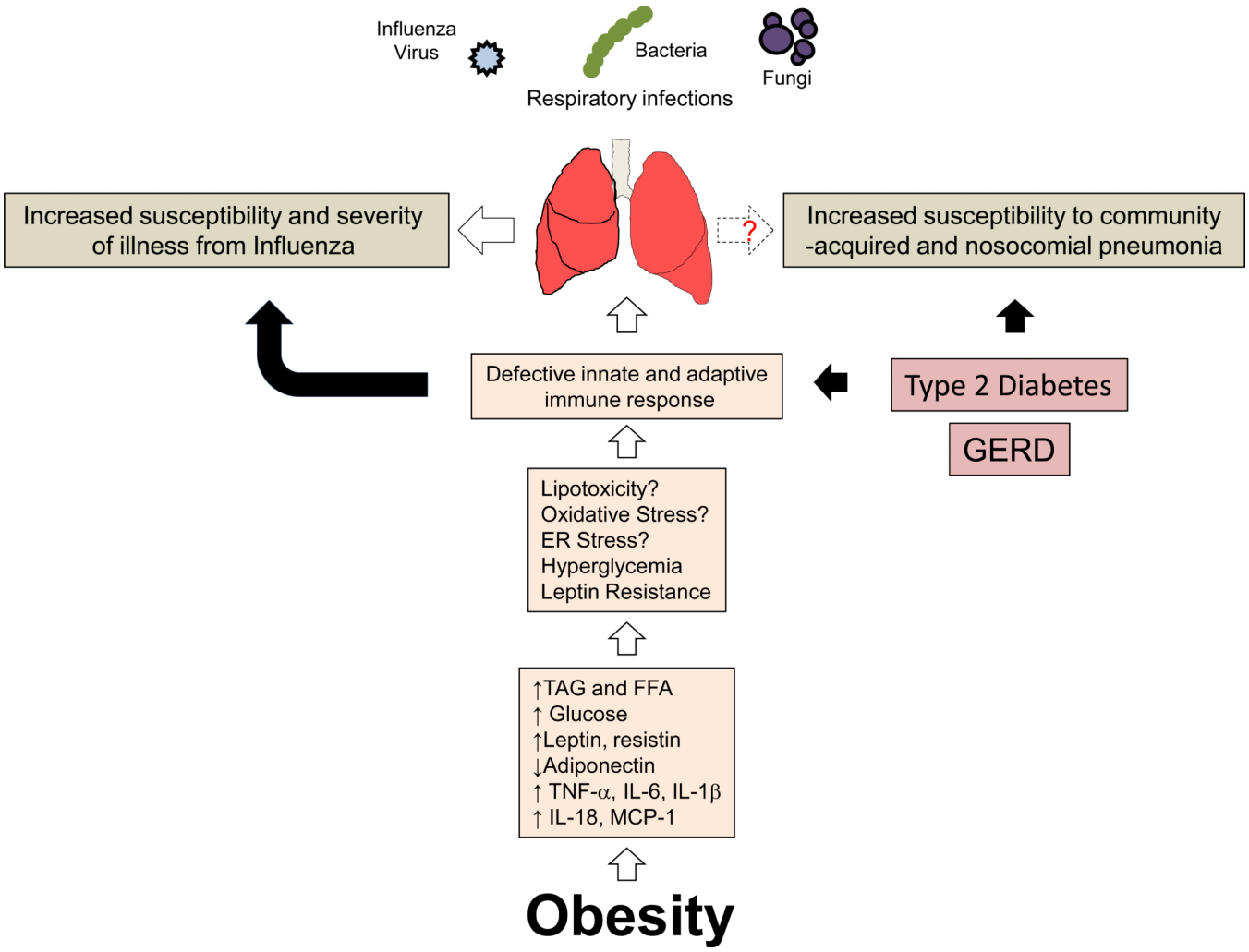

Figure 1.

Obesity weighs down host defense against pulmonary infections. Obesity diminishes pulmonary host defense against influenza and possibly bacterial and fungal pathogens. Excess adipose tissue in the obese results in numerous metabolic disturbances that contributes to a chronic state of low grade inflammation. The cause of which is due to elevated serum triacylglycerol (TAG), free fatty acids (FFA), hyperglycemia, and elevated proinflammatory adipokines such as leptin and resistin, and lower amounts of the anti-inflammatory adipokine, adiponectin, and classical cytokines, TNF-α, IL-6, IL-1β, IL-18, and MCP-1 are produced in greater quantities as adipose tissue expands. Collectively, these alterations result in defective innate and adaptive immune function that impair host against influenza infection. Whether or not obesity impairs host defense against bacterial pathogens is not clear. In addition, complications of obesity such as type II diabetes and gastroesophageal reflux disease (GERD) are known to impair host defense against viral, bacterial, and fungal pathogens.

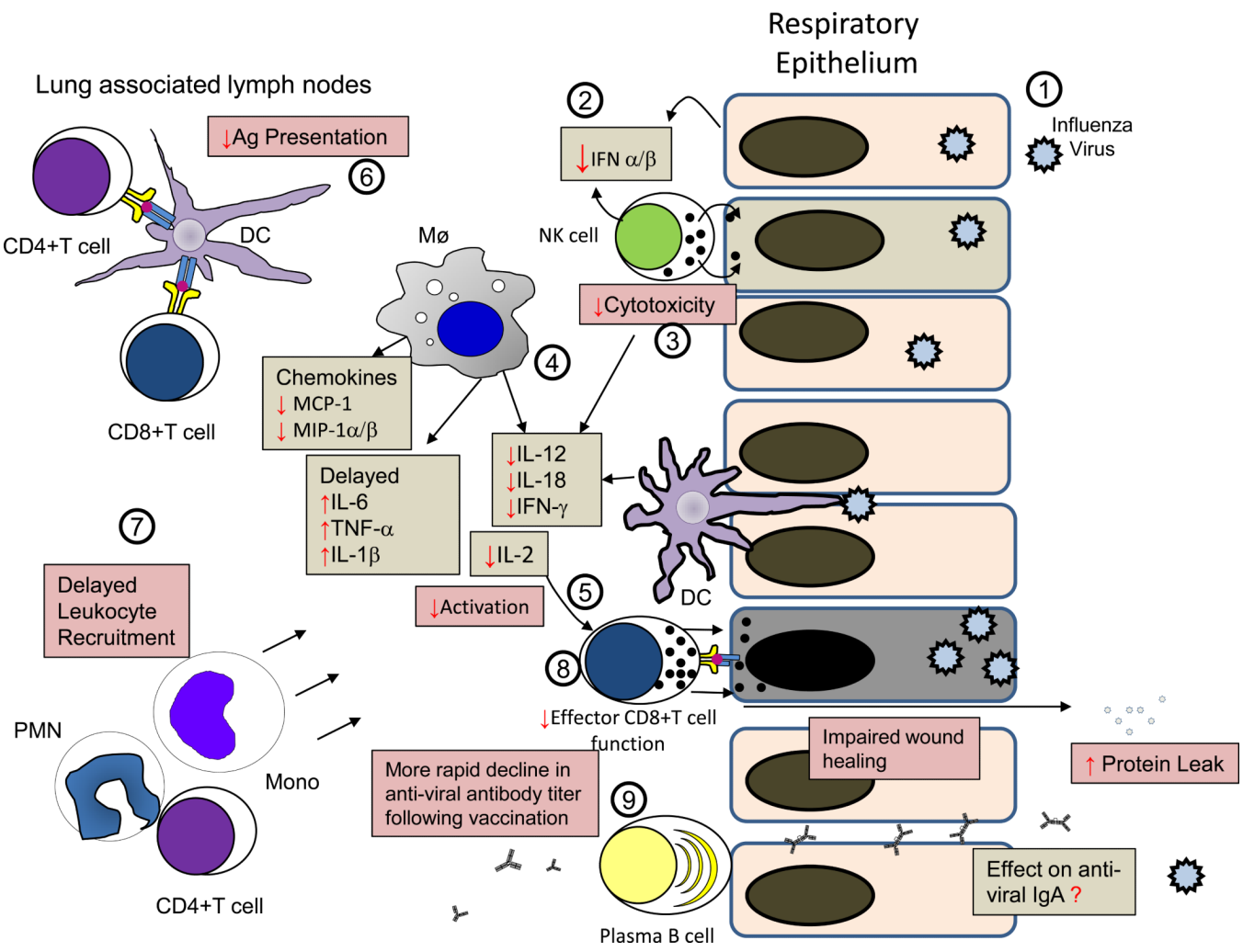

Figure 2.

Mechanisms by which obesity impairs host defense against influenza infection. This figure has been adapted and updated from a similar one published by Karlsson et al.[21]. Following infection of respiratory epithelial cells with the influenza virus (1), the elaboration of type I interferons (IFN-α/β) are reduced and delayed (2) and the cytotoxic response of natural killer (NK) cells (3) is attenuated in obese mice. The elaboration proinflammatory cytokines (IL-1β, IL-6, and TNF-α) (4) are delayed and increased and the production of cytokines (IL-12, IL-18, IFN-γ) produced by NK cells, macrophages (Mø), dendritic cells (DC) and IL-2 produced by CD4+ T cells, known to enhance the adaptive immune response is also reduced (5). Antigen presentation by DCs to CD4+ T helper and CD8+ T cells is also impaired (6). A delay in chemokine (MCP-1 and MIP-1α/β) production results in postponed recruitment of PMNs (PMN), CD4+ T cells, and monocytes (Mono) (7). The ability of effector CD8+ T cells to kill influenza infected cells is diminished and healing of pulmonary epithelial cells is also impaired resulting in increased microvascular permeability and protein leak (8). While a more rapid decline in antibody titers of obese humans following vaccination against influenza has been reported [36], it is not known if obesity affects IgA levels in the lung (9). The grey boxes indicate changes in cytokines and the pink boxes represent aberrant immune responses in the obese. Red arrows (↓ or ↑) indicate responses that are impaired or enhanced in the obese host.

Table 1

Association of obesity with severity of illness and death from pandemic H1N1 influenza of 2009

Reference Year	Country/year	Number of subjects	Comparisons	Odds ratios (95% confidence interval)	Association
MMWR[3] 2009	United States	10 patients, 3 deaths	None	NA	9 of 10 ICU patients admitted for severe H1N1 infection were obese
Vaillant[23] 2009	World wide	574 deaths	None	NA	Metabolic condition (including obesity) a risk factor for death
Jain[26] 2009	United States	272	General US population	NA	Obesity was an independent risk factor for hospitalization
Fuhrman[30] 2010	France	758 patients hospitalized with H1N1	Severe disease vs non-severe hospitalized adult cases	9.1 (4.4-18.7)	Obesity associated with severe disease

NA: Not applicable

Pulm Pharmacol Ther. Author manuscript; available in PMC 2014 August 01.

Table 2

Effect of obesity on community-acquired and nosocomial pneumonia.

Reference Year	Country	Number of patients	Comparisons	Odds ratios (95% confidence interval) or other	Association
Baik[46] 2000	United States	26,429 Men 78,062 Women	WT maintained vs 40 lb WT gain	M 1.46 (1.00-2.14) W 1.55 (1.15-2.10)	Increased risk of community acquired pneumonia
Jedrychowski 1998 [47]	Poland	1129 children	Low BMI with BMI≥20 (overweight children)	2.02 (1.13-3.59)	Increased risk of acute respiratory infection
Corrales-Medena[43] 2011	United States	317	BMI (under WT, normal WT, over WT, obese)	0.91 (0.84–0.98)	Increased BMI associated with lower 30-day mortality
Bochicchio[4] 2006	United States	1167	Non-obese vs obese	2.0 (1.02–3.76)	Increased risk of nosocomial pneumonia
Newell[6] 2007	United States	1543	BMI 18.5-24.9 vs 30-39.9, and ≥ 40	1.7 (1.21-2.44) 2.5 (1.48- 4.30)	Increased risk of nosocomial pneumonia
Yaegashi[7] 2005	United States	63	BMI 30-39.9 vs BMI ≥ 40	3% vs 33%	Increased risk for morbidly
Brant[52] 2001	Germany	500	Normal BMI 18.5-25 vs BMI≥30	3% vs 5%	No differences in risk of nosocomial pneumonia
Moulton[53] 1996	United States	2299	BMI	NA	No differences in risk of nosocomial pneumonia
Dossett[54] 2008	United States	1291	Normal BMI vs BMI 25- 29.9, 30-39.9, and ≥ 40	Obese 0.96 (0.64–1.4) Severely obese 0.89 (0.46–1.7)	No differences in risk of nosocomial pneumonia

WT: Weight, BMI: Body Mass Index

Pulm Pharmacol Ther. Author manuscript; available in PMC 2014 August 01.