Diabetes, Metabolic Syndrome and Obesity

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REVIEW

The Impact of Obesity on the Host–Pathogen Interaction with Influenza Viruses – Novel Insights: Narrative Review

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Abstract: After exposure to a viral pathogen, the host–pathogen interaction is essential to determine whether or not infection will ensue, and what the clinical outline of the infection will be. Recent research has shown that the patient with obesity presents a set of particular pathophysiological changes that lead to higher severity of viral infections, and this is particularly true for infection with influenza viruses. Herein, we describe the main metabolic, endocrine, and immune dysregulations that occur in the presence of obesity and their impact on driving intra-host viral diversity, leading to heightened severity and virulence of influenza. We show that obesity is linked to modified responses of both the innate and adaptive immune systems during viral infections, including influenza. Due to chronic inflammation and metabolic, endocrine, and signaling pathway disruptions, individuals with obesity have a suboptimal immune response. This results in longer illness duration, increased virus shedding, higher risk of hospitalization and complications, and greater mortality rates. Additionally, they may have a blunted response to vaccination and a higher likelihood of genetic mutation selection. Understanding the intricate interplay between obesity and viral pathogenesis is crucial for developing efficacious therapeutic approaches and public health policies, particularly in light of the escalating worldwide incidence of obesity.

Keywords: influenza, obesity, severity, metabolic syndrome, inflammation

Introduction

After exposure to a viral pathogen, the host-pathogen interaction is essential to determine whether or not infection will ensue, and what the clinical outline of the infection will be. In many instances, in immunocompetent hosts, exposure to a respiratory virus leads to self-limiting non-severe disease. However, certain host-specific factors can alter the host–pathogen interaction and facilitate more severe disease. Recent research has shown that the patient with obesity presents a set of particular pathophysiological changes that lead to higher severity of viral infections, and this is particularly true for infection with influenza viruses.

According to the World Health Organization (WHO), it is estimated that, in 2016, 39% of adults worldwide were overweight and 13% were obese.[1] A recent study from Spain shows an even higher prevalence in 2020, 55.8% for overweight status, and 18.7% for obesity in adults.[2] The data is also worrying in children, where up to 17% of those aged between 2 and 19 years are obese,[3] while in Romania, the prevalence of overweight children was reported at 7.5% and that of obese children at 18.5% in 2018.[4]

With the high worldwide prevalence of obesity, it has become essential to understand the main metabolic, endocrine, and immune dysregulations that occur during infection with influenza virus, as well as their impact on driving intra-host viral diversity, leading to heightened clinical severity and increased viral virulence.

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Influenza Infection in Humans: Clinical Expression and Impact of Obesity

The human host's response to influenza virus infection is not always effective and depends on factors such as age, comorbidities, genetic traits, and immune memory from previous exposure to antigens through vaccination or infection. This creates a complex and dynamic interaction between the host and influenza viruses, where host-specific factors play a crucial role. Increased susceptibility to infection, more severe forms of the disease, or both, can be seen in particular patient groups. As a result, specific risk groups for influenza have been identified by international consensus, for whom priority vaccination is recommended.

According to the European Centre for Disease Prevention and Control (ECDC), the groups at risk for severe influenza are older adults (aged 65 years and older) and all persons with comorbidities. These comorbidities include cardiovascular disease, chronic lung disease, diabetes, chronic liver disease, chronic kidney disease, neurological or neuromuscular pathology, obesity, physical disability, and immunosuppression.[5] The WHO also identifies pregnant women and those in the first two weeks postpartum, children under 59 months of age, and adolescents under 19 years of age on chronic salicylate therapy as risk groups.[6] The US Centre for Disease Prevention and Control (CDC) further includes patients with hematological conditions (eg, thalassemia), metabolic conditions (eg, genetic metabolic disease and mitochondrial disease), and patients with a history of stroke as additional risk groups for influenza complications.[7]

Obesity has been identified as a common comorbidity among patients hospitalized for influenza, with a prevalence ranging from 4.2% to 8.7%, following cardiovascular disease and diabetes.[8,9] This is often compounded by the coexistence of these conditions in the same patient, leading to an unfavorable outcome. Furthermore, obesity rates of up to 6.8% have been identified in the pediatric population hospitalized with influenza,[9] including young children under 5 years of age.

Influenza typically presents with systemic symptoms such as fever, malaise, headache, myalgia, fatigue, and respiratory symptoms such as cough, sore throat, and nasal congestion.[10] Fever is the predominant symptom in up to 90% of elderly patients and 97–99% of children[9,11] with a duration of approximately 5 days. Obese individuals also commonly experience fever during influenza, and the duration of the fever is significantly longer.[12] Although other symptoms have not been identified with significantly different frequencies compared to the non-obese population,[12] dyspnea has been reported more frequently in obese individuals. This is a sign of lower respiratory tract impairment and is associated with a higher risk of pneumonia.[13]

First Observations Regarding the Association Between Obesity and Severity of Influenza; Current Relevance

Obesity was first recognized as a specific risk factor for severity in the 2009 influenza A/H1N1 pandemic, when it was noticed that morbid obesity, defined as a body mass index (BMI) ≥40 was associated with a 2.8-fold increased risk of death from influenza and a BMI ≥45 with a 4.2-fold increased risk of death.[14] Subsequently, the broader association, beyond pandemic influenza, between obesity and seasonal influenza was also described, confirmed, and reconfirmed.

One of the important studies that confirmed this association between obesity and the risk of severe respiratory tract infections was that conducted in Canada by Kwong et al; they analysed adult patients, aged 18–64 years, in a cohort study that included 12 consecutive influenza seasons from 1996/97 to 2007/08. The study included 82,545 patients, totaling 105,035.6 person-years over the influenza seasons studied, and its main results indicated with a high degree of certainty that patients with obesity had a higher risk of severe forms of respiratory infections requiring hospitalization, as follows: class I obesity (BMI=30-34.9) 1.45-fold higher risk, class II or III obesity (BMI ≥35) 2.12-fold higher risk. Importantly, class II or III obesity retain their predictive value for severe respiratory disease even in patients with no other known risk factors, with a 5.10-fold increased risk.[15]

While the study referenced above had looked at medically attended respiratory illness, a recent meta-analysis included 35 papers that studied specifically only patients with confirmed influenza virus infection. It reconfirmed the role of obesity as a major risk factor for acquiring influenza (1.29-fold higher risk), for requiring hospitalization for influenza (1.62-fold higher risk) as well as for severe forms of influenza (1.56-fold higher risk) and for death from influenza (1.99-fold higher risk), respectively.[16]

Furthermore, a recent Mendelian randomization study has demonstrated that obesity is associated with an increased risk of acute or chronic respiratory diseases. Specifically, the study found that obesity is associated with an increased risk

of influenza (OR = 1.243), ranking third among acute diseases after acute unspecified lower respiratory infection (OR = 1.303) and acute bronchitis (OR = 1.252).[17]

The COVID-19 pandemic has posed important challenges,[18,19] and it has also highlighted the importance of studying obesity as a risk factor for respiratory disease. As with influenza, research has shown a strong correlation between obesity and the severity of SARS-CoV-2 infection. Therefore, the presence of obesity was found to be correlated with the severity, duration of hospitalization, progression to respiratory failure, admission to intensive care, need for mechanical ventilation, and COVID-19 mortality, with a direct correlation to the BMI value.[20–22] Additionally, the COVID-19 pandemic has resulted in increased rates of obesity in the general population.[23,24] Therefore, given the rising rates of obesity and the renewed circulation of influenza viruses at levels comparable to pre-pandemic times,[25] it is crucial to comprehend how the clinical picture of influenza is affected in overweight patients. Clinicians must be mindful of the important risks that influenza associates in patients with obesity and take timely measures for risk mitigation. Establishing effective management requires a thorough understanding of the underlying pathophysiological mechanisms.

Dysregulations Specific to the Obese Host Alter Its Interaction with Influenza Viruses and Drive Clinical Severity and Viral Virulence

The observed associations mentioned above between obesity and heightened severity of influenza are explained by a set of highly complex pathophysiological mechanisms that derive from a set of important metabolic, endocrine, and immune changes specific to the patient with obesity, which we aim to describe below, in the light of the latest published data.

Metabolic Dysregulation

The most well-studied obesity-induced dysregulations occur in the metabolic system, with a clear association between obesity and insulin resistance, glucose intolerance that can progress to diabetes mellitus, dyslipidemia, and cardiovascular disease, all culminating in metabolic syndrome.[26] Conversely, patients with diabetes mellitus have two-fold higher odds of associating obesity, and are particularly affected by influenza.[27] Obesity in itself induces a number of important changes at the metabolome level; these include alterations in the N-acyltransferase pathway and in a set of fatty acid and nucleotide pathways, which are expressed by increases in the following metabolites in the lung: P-cresol sulphate, glutamyl-proline, tetrahydrocortisol, 3-hydroxybutyric acid, and multiple species of acyl-carnitine.[28]

Increased free fatty acid levels are part of the main changes associated with obesity, studied in large cohorts of patients, where a 26% increase compared to a non-obese population was reported, and this is considered to be one of the determinants of insulin resistance.[29]

This particularity of the obese host influences the interaction with influenza viruses directly, viral replication being amplified in the presence of increased lipid content in fatty acids,[30] but also indirectly, through the role of fatty acids as signaling molecules for immune cells.[31]

Almond M. et al conducted a study on the correlation between dysregulated cholesterol levels and increased leptin concentrations in both upper and lower airways of obese individuals. The study found a negative correlation between leptin concentrations and the induction of interferon (IFN) synthesis, regardless of influenza virus subtype. Additionally, the study found a positive correlation between leptin values and bronchial adenosine monophosphate (AMP) levels. Therefore, it seems that the disturbance of fatty acid metabolism leads to the dysregulation of antiviral immunity in the respiratory tract.[32]

In overweight individuals, levels of essential fatty acids, including long-chain saturated fatty acids and ω-6 polyunsaturated fatty acids, are affected.[33,34] Arachidonic acid (AA) is one of the most important of these fatty acids, and it has been shown to play a role in the pro-inflammatory response during viral infections.[35] Chandrasekaran R. et al conducted a study on obese mice and found that elevated lung levels of AA induced a strong cytokine response in human bronchial epithelial cells when exposed to influenza A viruses. Furthermore, obesity in these mice resulted in increased activation of the AA-p38 mitogen-activated protein kinases (MAPK) pathway after infection with influenza A viruses. Suppression of this pathway decreased inflammation, lesions, and improved survival rates.[36] Particularly, the p38 MAPK is essential for generating inflammatory cytokines, as well as for the replication of viruses.[37]

Another important issue that arises as a result of metabolic dysregulation in obese patients is the impaired resolution of inflammation.[38] Normally, during the quenching of the inflammatory process, there is a shift in lipid classes, characterized by a reduction in the production of AA-derived mediators, along with a simultaneous increase in compounds known as specialized proresolving mediators (SPMs) also derived from essential fatty acids.[39] The deficiency of SPM, which was identified in obese mice, leads to prolonged viral replication and an inflammatory process.[40,41]

Endocrine Dysregulation

Obesity also dysregulates the endocrine system on multiple levels. For example, part of a wider meta-inflammatory status specific for obese patients, chronic inflammation of the pituitary gland has been reported.[42] This is one of the main endocrine glands that also plays a role in modulating the immune response to infection, mainly by regulating lymphocyte differentiation processes.[43] Growth hormones and prolactin are essential for lymphocyte maturation, for ensuring the ability of lymphocytes to respond to antigen presence, and for maintaining the immunocompetence status.[43]

Other endocrine glands that are affected in obesity are the thyroid and adrenals. The association between thyroid damage and obesity is bidirectional. On the one hand, hypothyroidism stimulates weight gain, but the reverse has also been described, namely the induction by obesity of a degree of secondary hypothyroidism, with a decreased level of free thyroxine (fT4) and an increased level of thyroid stimulating hormone (TSH), as well as a degree of autoimmunity at the thyroid level, mainly determined by leptin produced by excessive numbers of adipocytes.[44] Thyroid hormones are important regulators of lymphocyte signaling at the nuclear level as they control nuclear transcription factors; TSH also plays a direct stimulatory role in immunoglobulin secretion and interleukin (IL)-2 production,[43] and hypothyroidism has been described to be associated with the induction of a degree of immunosuppression.[45]

Glucocorticoid metabolism is also altered in obesity, with lower cortisol levels in the liver but higher in adipose tissue.[46] Glucocorticoids are considered immunosuppressive hormones, and play an important role in cytokine production,[43] which is why altered glucocorticoid levels in the presence of obesity may affect the regulation of immune processes.

Another important aspect to discuss is related to the negative impact of obesity on serum testosterone levels.[47,48] Similarly, hypotestosteronemia leads to increased adipose tissue mass. Thus, a vicious circle is created, in which the two imbalances mutually maintain each other.[47,48] Low testosterone levels have been associated with a poor immune response to influenza infection. Studies in murine models have shown that testosterone supplementation in females[49] or elderly males[50] can protect against severe influenza by modulating the pro-inflammatory response in their lungs.

At the same time, it is known that white adipose tissue has an intense endocrine activity and secretes numerous hormones and metabolites.[46] Thus, in adipose tissues collected from murine models infected with influenza virus, elevated levels of proinflammatory cytokines have been identified, as well as elevated levels of leptin.[51] In addition to what has been previously discussed about leptin, it is known to play an essential role in regulating the interaction between energy metabolism and the immune system, due to the presence of its receptor throughout the immune system.[52] Also, the contribution of pre-existing high levels of leptin to the development of severe lung injury has been documented in mouse studies.[53]

Overall, there is a co-influencing, looping relationship between overweight and endocrine disruption that alters metabolic and immune responses, with major impact during acute infections such as influenza.

Meta-Inflammation and Immune Dysregulation

Ample studies in murine obesity models have identified a degree of persistent inflammation associated with obesity. For example, in the adipose tissue, an increased influx of immune cells has been described, predominantly for monocytes, granulocytes such as neutrophils, mast cells, basophils, but also for CD4 T helper-1 lymphocytes, CD8 lymphocytes, and natural killer cells, in parallel with decreased levels of eosinophils, regulatory T lymphocytes, and T helper-2 lymphocytes.[54] In addition, CD4 and CD8 T cells express reduced numbers of CD69, CD28, CD40 ligands and decreased production of IFN-γ and granzyme B, suggesting deficiencies in T cell activation and function.[55] In parallel, levels of pro-inflammatory cytokines such as tumor necrosis factor (TNF)α and IL-1β, levels of non-esterified free fatty acids and acylcarnitines are increased,[54] and so is the release of reactive oxygen species from adipose tissue.[54,56]

This pro-inflammatory status is also found in the respiratory tract of the obese host. Murine obesity models have shown that influenza virus infection leads to a marked cellular infiltrate in the lung, initially monocytic in the first days

after infection, and subsequently neutrophilic,[57] but with lower levels of macrophages and regulatory T cells.[28,54] These changes have been attributed to increased lung levels of granulocyte colony-stimulating factor (G-CSF), CXCL10, CXCL1, and monocyte chemoattractant protein-1 (MCP-1), as well as IL-6, which is known to play a pro-inflammatory role.[57] In parallel, decreases have been reported in transforming growth factor (TGF)-β,[57] which normally plays a key role in modulating the pro- and anti-inflammatory response,[58] as well as in the levels of IFN-γ,[57] which is involved in the innate and the adaptive immune response to infection, but which also plays a complex role in modulating inflammatory status.[59] These changes occurring during the pathogenesis of influenza infection are associated with increased permeability of the alveolar-capillary barrier and with a longer persistence, above 14 days, of the inflammatory process in the lungs, compared to non-obese murine models, in parallel with a marked decrease in epithelial regeneration.[57]

This high degree of immunopathological damage is also associated with high influenza mortality in murine models of obesity[56,57] – Figure 1. Importantly, all these changes have been described for both genetically induced obesity and diet-induced obesity, but this increased severity of lung damage in the presence of obesity can be prevented by early administration of antiviral treatment, and the role of high-dose oseltamivir in preventing severe forms of influenza has been studied.[57]

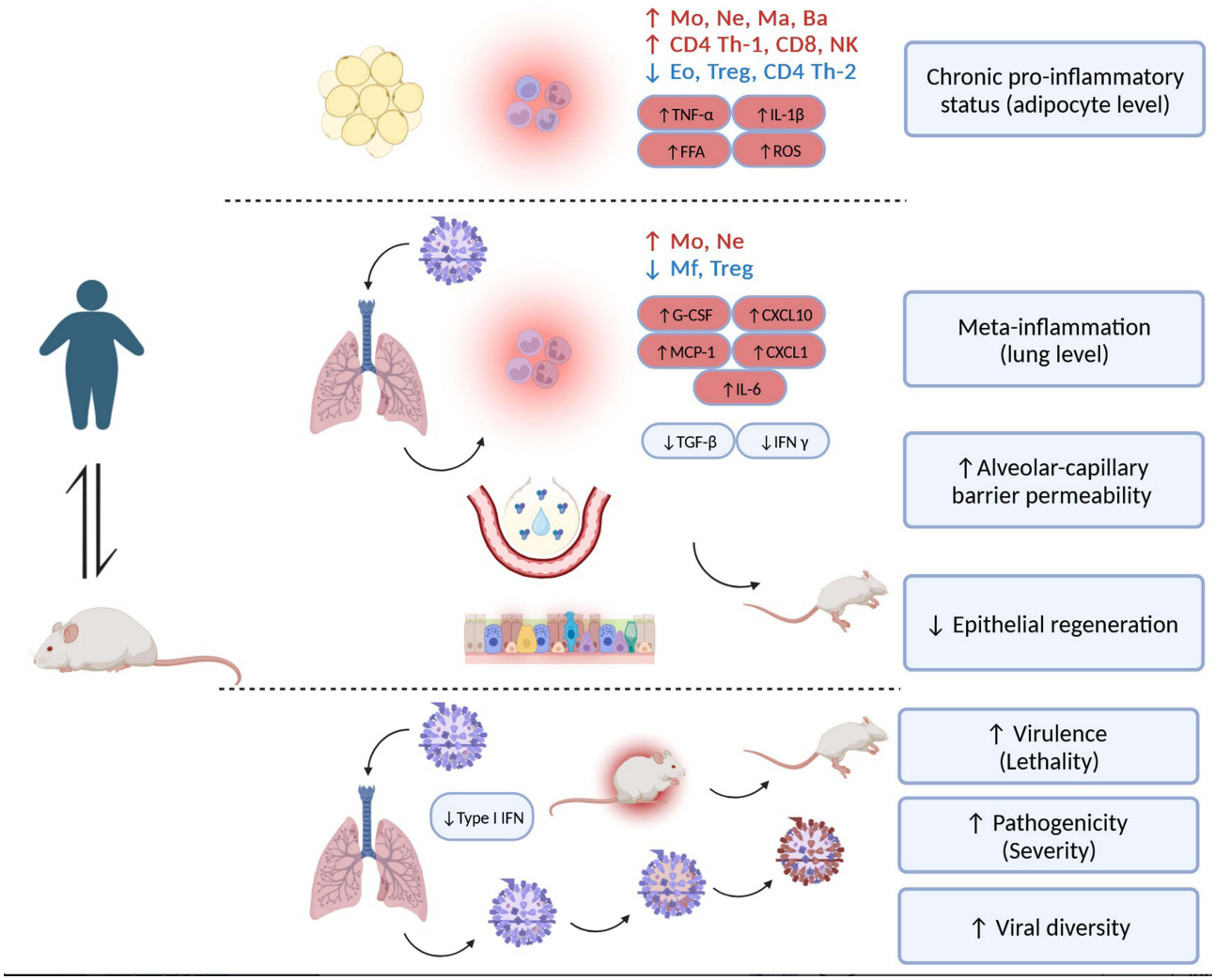

Figure 1 Pathogenesis of influenza virus infection in obese hosts-specific dysregulations in adipocytes, lungs and in the overall pathogen–host interaction (figure created with BioRender.com).

Abbreviations: Mo, monocytes; Ne, neutrophils; Mf, macrophages; Ba, basophils; Th, T helper; NK, natural killer cells; TNFα, tumor necrosis factor α; IL, interleukin; FFA, free fatty acids; ROS, reactive oxygen species; Treg, regulatory T cells; G-CSF, granulocyte colony-stimulating factor; MCP-1, monocyte chemoattractant protein-1; TGF-β – transforming growth factor β; IFN, interferon.

The Obese Host Provides an Environment Conducive for the Selection of Virulent Influenza Strains

Patients with obesity and symptomatic influenza A have a 42% longer duration of influenza A virus shedding compared to patients without obesity, whereas patients with obesity and paucisymptomatic or asymptomatic influenza A virus infection have a 104% longer duration of virus shedding.[60] This phenomenon indicates, on the one hand, a higher contagiousness of obese patients with influenza, and, on the other hand, creates the prerequisites for viral mutation selection through prolonged viral replication under conditions of low immune pressure.

To ascertain this phenomenon, Honce et al recently studied influenza A/California/04/2009 infection in murine obesity models, and found that as soon as 3 days post-infection, intra-host viral diversity was increased in the lungs in the obese host, and selection of virulence-associated mutations was favored.[61] Moreover, Honce et al reported that serial inoculation of influenza virus isolated from obese murine models selected influenza virus strains with higher replication as well as higher pathogenicity, expressed by higher clinical severity starting with the third viral passage, as well as higher virulence expressed by higher mortality coupled with a lower mean lethal dose 50%, phenomena that did not occur in non-obese hosts[61] (Figure 1). They further went on to study the main mechanism that allows selection of these influenza virus strains with increased pathogenicity and virulence, and they found a decrease in type I IFN signaling, with decreased expression of genes responsible for induction and signaling through the IFN pathway, a phenomenon that occurs within the first 8 hours following influenza virus infection.[61] To confirm the relevance of these observed phenomena in murine models to the human host, Honce et al also confirmed these experiments in vitro on human bronchial epithelium from obese donors.[61] Other recent research on avian variants of the influenza virus (H9N2) has identified increased positive selection on de novo mutations in obese murine subjects, resulting in a variety of non-synonymous changes.[62]

The analysis of the efficacy of antiviral treatment revealed that the use of oseltamivir did not positively impact virus clearance in obese mice, and no resistance mutations were identified. However, it led to phenotypic resistance in vitro.[63] This suggests the need for careful surveillance of pharmaceutical interventions in obese patients with influenza, as well as monitoring for possible resistance mutations in the neuraminidase gene.

These findings are crucial in clinical practice and epidemiological surveillance of influenza viruses. It is necessary to establish correct management rapidly and limit human-to-human transmission in hosts with obesity to prevent the accumulation of influenza virus mutations.

Suboptimal Coverage of Influenza Vaccination Among Obese Patients

Vaccination is the main instrument available for preventing influenza; however, its yearly uptake is in most countries less than optimal. Patients with comorbidities are among the most important at-risk categories and are prioritized for influenza vaccination, according to the most important regulatory authorities, including the WHO and the ECDC. While obesity in itself does represent a comorbidity, recent studies have shown that in most cases it is not perceived as such and that influenza vaccination uptake is 71% lower among patients with obesity, compared with other risk categories,[64] and 24% lower compared to that of non-obese patients.[65] A study conducted in Spain found that obese adults had a lower rate of influenza vaccination compared to adults with other comorbidities. When vaccinated, they were more likely to have other chronic conditions, particularly diabetes, cardiovascular disease, or chronic lung disease.[62] Similarly, among the pediatric population, Karachaliou et al recently demonstrated that obese children had significantly lower rates of influenza vaccination compared to the general pediatric population; by the age of 4, only 13.3% of obese children were vaccinated compared to 37% of the general population, and by the age of 10, only 2.9% of obese children were vaccinated compared to 40% of the general population.[66] For these reasons, it is important to study the determinants of vaccine uptake for each specific risk group, in order to better address each gap in vaccination coverage with a targeted and tailored approach.[67–69]

Inadequate Response to Influenza Vaccination in the Obese Host

Inadequate response to 2009 A/H1N1 vaccination has been described in murine obesity models, with lower levels of vaccine-generated antibodies, lower neutralizing activity,[70] as well as lower levels of influenza virus-specific memory CD8 T lymphocytes.[71] This inadequate response is at least partly explained by the obesity-induced chronic pro-

inflammatory status, expressed by elevated serum and adipocyte MCP-1 levels, and has been associated with a more severe pathogenesis of pulmonary inflammatory damage following influenza exposure in the presence of obesity, even after vaccination.[71] Obesity has recently been shown to induce B-cell dysfunction similar to that seen in the aging process, thus post-vaccination-induced hemagglutinin-specific inhibitory antibody titers were reduced in overweight individuals, while proinflammatory cytokine and autoimmune antibody levels were elevated.[72] Additionally, Neidich et al showed that although some adults with obesity may have an effective response to vaccination, they are twice as likely to develop influenza compared to non-obese adults.[73] Among children, the presence of adiposity does not appear to significantly alter the specific antibody response, and vaccine efficacy is similar to that among children of normal weight for age.[74,75]

Conclusion

In conclusion, there are multiple pathophysiological mechanisms that occur in the obese host and that alter their interaction with influenza viruses, leading to more severe infection and to the selection of more virulent viral variants. These can include altered immune responses, such as changes in the activity and effectiveness of various immune cells, and may contribute to a higher risk of complications and prolonged illness. A good understanding of these mechanisms is important in order to better guide timely treatment intervention and to potentially develop tailored approaches to the management of influenza in the obese patient.

Disclosure

The authors report no conflicts of interest in this work.

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