Influenza and Obesity: Will Vaccines and Antivirals Protect?

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(See the article by Kim et al, on pages 244–51, and the article by O’Brien et al, on pages 252–61.)

There is a worldwide pandemic of obesity. The World Health Organization estimates 500 million adults and almost 43 million children under the age of 5 years to be obese (body mass index >30) [1]. According to the Centers for Disease Control and Prevention, nearly one-third of the adult US population is obese. Obesity has been definitively linked to a wide range of comorbidities, including increased coronary heart disease, type 2 diabetes, hypertension, and dyslipidemia [2]. Beyond the contribution of obesity to these chronic diseases, surprisingly little attention has been given to the effects of obesity on the immune response to infectious diseases.

Several studies have now reported that obesity was associated with a poor outcome following infection with 2009 pandemic influenza (pH1N1) [3–7]. Kwong and colleagues reported that obese individuals, in addition to being at risk from pH1N1, were also at greater risk for hospitalization from seasonal influenza infection [8]. In sum, these reports demonstrate that obesity increases the risks associated with influenza infection.

Beyond these clinical studies on the role of obesity in influenza infection, 2 studies in this issue of the Journal using a mouse model and pH1N1 infections provide new insights into obesity’s effect on the immune response to influenza virus infection and the ability of vaccination or antiviral treatment to mitigate the effects of infection.

Vaccination remains our best intervention to prevent influenza virus infection. If obesity impairs the immune response to influenza vaccination, then a highly vulnerable population will not be fully protected. Indeed, several studies show that the response to hepatitis or tetanus vaccination may be suboptimal in obese individuals [9–11]. The article by Kim et al in this issue of the Journal uses a vaccination model in diet-induced obese mice. Kim et al found that obese mice vaccinated with commercial monovalent pH1N1 vaccine were not protected from pH1N1 infection. Although 86% of the vaccinated lean mice survived a challenge infection, no immunized obese mice survived beyond 12 days. This remarkable finding, if applicable to humans, is sobering. Kim et al also reported that obese mice had higher lung viral titers, increased lung pathology, and increased expression in lungs of mRNAs for proinflammatory cytokines and chemokines. In obese mice, neutralizing antibody levels were significantly diminished 1 week after a third immunization. Thus, influenza vaccination of obese mice did not prevent infection, and once infected, obese mice had greater lung pathologic changes, including increased inflammation, compared with lean mice. The mechanisms underlying the more severe infections need to be determined.

Other laboratories have used obese mice (both genetically and diet-induced) to study the immune response to influenza virus infection. Our laboratory has demonstrated that diet-induced obese mice infected with influenza A/Puerto Rico/8/34 (PR8, a mouse-adapted strain of influenza virus) have greater morbidity and mortality following infection [12, 13]. This response in obese mice is associated with reduced natural killer cell activity, poor dendritic cell processing and presentation of viral antigens, and impaired CD8+ T-cell function. In lean mice, primary infection with influenza X31 followed by a challenge infection with a lethal dose of PR8 resulted in full protection; however, in obese mice, this regimen failed to protect the mice and resulted in increased mortality and morbidity [14]. In this model, obesity was associated with impaired generation, maintenance, and function of memory T cells [14, 15]. Notably, this mouse model is only applicable for T-cell responses, not for antibody responses. The mechanistic basis for increased mortality in obese animals was not determined.

The article by O’Brien et al in this issue of the Journal proposes a novel hypothesis for increased lung pathology found in influenza virus–infected obese mice. O’Brien et al used both genetically obese mice (ob/ob) and diet-induced obese mice and infected them with pH1N1 and an
H3N2 strain (A/Hong Kong/1/1968, HK68). As shown previously for PR8 virus infection, obese mice had increased mortality and increased lung pathology but no increase in viral titers compared with lean animals. Increased cellular infiltration, including monocytes, neutrophils, and CD8+ T cells, was found in the lungs of obese mice compared with lean infected mice. O'Brien et al suggest that increased cellular infiltration reflected increased levels of chemokines in lungs of obese infected mice. Infection with either pH1N1 or HK68 had similar effects. Because lean and obese mice cleared virus by day 10 postinfection and viral titers did not differ in obese and lean mice, it is likely that the greater severity of disease in obese mice was not caused by higher viral titers. This finding is inconsistent with the report of Kim et al of higher viral titers in lungs of obese mice compared with those in lean mice. This difference could reflect heterogeneity in the pH1N1 strains used for infection in the 2 studies and/or disparities in inoculating doses.

O'Brien et al also found a marked reduction in epithelial proliferation in lungs of infected obese mice. Recovery of lungs from influenza virus infection includes regeneration of damaged epithelium and resolution of inflammation. At 14 days postinfection, lungs of obese mice were still inflamed but inflammation had resolved in lungs of lean animals. Compared to lean animals, epithelial regeneration was severely impaired in the obese mice: increased protein levels in bronchoalveolar fluid from obese mice indicated barrier dysfunction. Indeed, obese mice had significantly more lung edema after influenza infection compared with lean animals. This suggests that obesity impairs wound repair in lungs of influenza-infected mice, although the relation between obesity and altered repair is unknown.

In addition to influenza vaccination, the antiviral agent oseltamivir is often used to prevent or treat pH1N1 infection. O'Brien et al treated obese and lean mice with oseltamivir before and during pH1N1 infection. Both obese and lean mice treated with weight-adjusted dosages of the drug showed reduced lung inflammation and similar rates of epithelial cell regeneration rates and were completely protected from influenza mortality. Because viral titers did not differ between untreated lean and obese mice, yet treatment with oseltamivir could still protect the obese animals from lethal infection, it appears that some interaction between the obesogenic environment and the virus results in increased pathogenicity in obese mice and this can be affected by oseltamivir.

Taken together, these 2 papers provide important new information about the consequences of influenza infection in obese mice. Studies of the pathogenesis of influenza in mice have often been useful for identifying potential outcomes in humans infected with this virus. The possibility that influenza vaccination is not fully protective in obese humans has significant implications for public health. Similar responses to antiviral treatment in obese and lean mice may provide a tool to protect obese individuals who do not respond fully to the influenza vaccine and may be a starting point for additional studies of the host defense mechanisms that are altered by obesity. The growing global obesity epidemic and the constant threat of an influenza pandemic necessitate that obesity should be regarded as an independent risk factor, much like advanced age, and that current vaccine strategies may need to be adjusted for this population.

Notes

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