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
tion. 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 dos-
ages of the drug showed reduced lung
inflammation and similar rates of epithe-
lium 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 en-
virenment and the virus results in in-
creased 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 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.

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