Association between H1N1 Infection Severity and Obesity—Adiponectin as a Potential Etiologic Factor

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Seasonal influenza virus infection affects a large proportion of the population and is associated with mortality in certain population groups. The recent H1N1 influenza virus has been characterized as pandemic, and it appears to have a distinct pattern in terms of the population that is affected. Multiple studies analyzing the patient profile in the H1N1 pandemic have indicated that obesity is strongly associated with severity of disease [1–4]. Indeed, independent studies from several countries have shown that a large fraction of individuals infected with H1N1 who were admitted to an intensive care unit (ICU) had an increased body mass index (typically >30) and that the morbidity rate among all obese patients who were admitted to an ICU with H1N1 infection was increased [2–4]. Although the risk of complications, including severe infection, in ICUs is increased in obese patients [5], recent studies on H1N1 infection have shown that the severity of the response to the virus is strikingly increased in this population. Obesity as a risk factor for influenza-associated critical illness has not been described in previous pandemics or in seasonal influenza epidemics.

Obesity results in altered lung mechanics and physiology [6, 7]. Increased airway resistance, impaired gas exchange, and chronic inflammation of the respiratory tract are encountered in morbidly obese patients [6, 7], and these are factors that could affect the outcome of acute lung injury after H1N1 infection. In addition, obesity is associated with important changes in the immune system. Adipocytes—the cells that primarily compose adipose tissue—are now known to produce factors, called adipokines, that can significantly alter inflammatory cell and immune function. Adipocytes produce cytokines, growth factors, and adipokines that promote macrophage activation. Adiponectin—an adipokine that reduces macrophage activity and proinflammatory cytokine production—is produced in decreased amounts in obese patients. These activated macrophages produce increased levels of interleukin 6 and tumor necrosis factor α as well as reactive oxygen species, which contribute to the chronic proinflammatory state associated with obesity. As a result, obesity is characterized by sustained low-grade inflammation and altered responses to infection [5]. Obese individuals exhibit increased sepsis-related morbidity, possibly related to an increased responsiveness to pathogens that results in a cytokine storm and a reduced ability to mount an effective response to nosocomial infections. Animal models of infection have shown that obesity alters susceptibility to infection and sensitivity to proinflammatory stimuli [8–10].

Several mechanisms have been proposed to link inflammation and obesity. The adipose tissue of obese individuals appears to be inflamed and is a source of proinflammatory mediators. In addition, adipocytes produce adipokines, which also affect immune cells directly or indirectly. Among adipokines, leptin is considered to be proinflammatory and is elevated in obese individuals, whereas adiponectin production is inversely correlated with body mass index. The anti-inflammatory action of adiponectin is partly attributed to the induction of interleukin 10 and the suppression of nuclear factor κB in macrophages and, thus, to the suppression of T cell–mediated responses and innate immune responses, respectively. In addition, adiponectin has been shown to directly modulate the expression of interleukin 1 receptor–associated kinase M (IRAK-M), an inactive homologue of IRAKs that acts as dominant negative inhibitor controlling the responsiveness and tolerance of macrophages to proinflammatory stimuli [11]. As a result, the innate immune system of individuals who have low plasma levels of adiponectin is hyperresponsive to pathogens, compared with the innate immune system of individuals who have high...
plasma levels of adiponectin [11]. Thus, the response of an obese person to H1N1 infection is more pronounced than that of a lean person, and levels of proinflammatory mediators are elevated. The absence of these negative-feedback mechanisms may allow the initiation of a cytokine storm and the development of septic shock. This model is outlined in Figure 1.

Of interest, pregnant women are another group at risk for severe—even fatal—H1N1 infection [12]. Adiponectin levels are low in these patients as well [13, 14]. Therefore, we can hypothesize that individuals with low plasma levels of adiponectin—including obese persons, pregnant women, and those with metabolic syndrome—are more likely to overreact when infected with H1N1. Indeed, elevated levels of proinflammatory as well as type 1 and type 17 T helper cytokines have been observed in H1N1-infected individuals [15, 16]. Whether obese or pregnant patients have higher levels of these cytokines is unknown at present. However, the increased severity of disease observed in these groups suggests such a possibility. Whether the resulting cytokine cascade is the consequence of direct infection of lung epithelial and immune cells (or even adipocytes) by H1N1 virus [17] or is a secondary event stemming from an increased rate of bacterial superinfection is unclear and requires further study.

**References**