Minireview

Effect of adenovirus and influenza virus infection on obesity

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ABSTRACT

The purpose of this review is to provide an overview of the effects of adenovirus and influenza virus infections on obesity in various experimental models. We reviewed studies that were conducted within the past 10 years and were related to virus infection and obesity prevalence. Here, we discuss a different causal relationship between adenovirus and influenza infections with obesity. Adenovirus infection can cause obesity, whereas obesity can be a risk factor for increasing influenza virus infection and increases the risk of morbidity and mortality. The prevalence of obesity due to adenovirus infections may be due to an increase in glucose uptake and reduction in lipolysis caused by an increase in corticosterone secretion. Adenovirus infections may lead to increases in appetite by decreasing norepinephrine and leptin levels and also cause immune dysfunction. The relationship between obesity and influenza virus infection could be summarized by the following features: decreases in memory T-cell functionality and interferon (IFN)-α, IFN-β, and IFN-γ mRNA expression, increases in viral titer and infiltration, and impaired dendritic cell function in obese individuals. Moreover, leptin resistance may play an important role in increasing influenza virus infections in obese individuals. In conclusion, prevention of adenovirus infections could be a good approach for reducing obesity prevalence, and prevention of obesity could reduce influenza virus infections from the point of view of viral infections and obesity.

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Contents

Introduction

When a person's energy intake is higher than the energy expenditure, it can lead to the person becoming obese or overweight (Hur et al., 2013). The excessive intake of nutrients can alter an immune response directly or indirectly by affecting an individual's metabolic and endocrine status (Samartín and Chandra, 2001). Moreover, immune dysfunction is accompanied by an increased rate of infection (Martí et al., 2001) because immunocompetence depends on a person's nutritional status and can be easily dysregulated in conditions caused by imbalanced nutrition, such as obesity (Karlsson and Beck, 2010). A decade ago, Dhurandhar et al. (1997) were the first to demonstrate that a virus infection could be linked to human obesity and postulated that avian adenovirus infection may have contributed to the worldwide epidemic of obesity. During the recent pandemic of influenza A/H1N1/2009, obesity was recognized for the first time as an independent risk factor for increased influenza morbidity and mortality (Louie et al., 2011).

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O'Shea et al. (2010) reported that obese individuals have decreased circulating natural killer (NK) cell populations with diminished activity. Moreover, obesity produces a chronic inflammatory state associated with dysregulated cytokine production, reduced NK cell activity, altered CD4:CD8T cell balance, and a decreased response to antigen stimulation, which could affect responses to vaccination (Talbot et al., 2012). Akiyama et al. (2011) also reported that NK cell levels were significantly lower in obese subjects than in lean controls and animal models. Specifically, in diet-induced obese mice which underwent H1N1 influenza challenge, both the production of IFN-γ and number of influenza-specific memory T-cells significantly reduced; furthermore, 25% of the mice died, compared to 0% mortality in control mice. Although the cause of obesity has been considered to be multifactorial, the concept of obesity having a viral origin has been relatively understudied compared to genetic and behavioral causes (Gabbert et al., 2010). Therefore, knowledge regarding the mechanisms underlying the effects of viral infection on the occurrence of obesity is very useful in preventing obesity or viral infections. Therefore, the purpose of this review is to provide an overview of the effects of adenovirus and influenza virus infections on obesity in various experimental models.

Obesity and virus infection

We reviewed the literature regarding the effect of immune systems and virus infections on obesity. In order to obtain a complete and current update on the published literature that covered significant findings, searches in Pubmed, Medline, Scopus, and Google Scholar (1990 to 2013) were performed using the following medical subject headings terms and keywords: obesity, immune, virus infection, adenovirus and influenza virus.

A number of scientists have reported that viruses, such as adenovirus 36, play an important role in the development of obesity. The adenovirus can infect immature adipocytes (Pasarica et al., 2006). Consequently, adipocytes can grow quickly and multiply faster, resulting in increased body weight (Dhurandhar et al., 2002). Moreover, the risk of infections with viruses, such as the influenza H1N1 strain, is more severe in obese individuals than in those with normal body weight (Karlsson et al., 2010). In this review, we found that the development of obesity, especially the growth of fat, resulting from viral infection is closely related to the immune response to viruses, such as the regulation of cytokines and CD8 + T-cells. Obesity causes a chronic inflammatory state associated with dysregulated cytokine production, reduced NK cell activity, altered CD4:CD8T cell balance, and a decreased response to antigen stimulation, which could affect responses to vaccination (Talbot et al., 2012). Obese individuals have been shown to have decreased circulating NK cell populations with diminished activity (O'Shea et al., 2010). Thus, we can assume that the reasons for the relationship between virus infection and obesity prevalence may be related to decreases in immunity and nutritional imbalance.

Obesity results in altered lung mechanics and physiological features (McCallister et al., 2009). Obesity can profoundly alter lung mechanics; diminish exercise capacity; augment airway resistance, making it harder to breathe; and influence respiratory muscle function, control of breathing, and exchange of gas (Falagas and Kompoti, 2006). In general, obese patients allocate a disproportionately high percentage of total body oxygen consumption to respiratory work, resulting in a reduced functional residual capacity and expiratory volume (Flegal et al., 2005). Subsequent ventilation–perfusion abnormality can decrease the ventilatory reserve and predispose the obese to respiratory failure and even mild pulmonary challenges (Flegal et al., 2005). Moreover, increased airway resistance, impaired gas exchange, and chronic inflammation of the respiratory tract are encountered in morbidly obese patients (McCallister et al., 2009) and could affect the outcome of acute lung injury after H1N1 infection (Tsatsanis et al., 2010). Therefore, excess adipose tissue deposition may result in the dysfunction of respiratory organs and increase the risk of viral infection.

Adenovirus and obesity

Adenoviruses are a family of icosahedral, nonenveloped, double-stranded DNA viruses with diameters ranging from 65 to 80 nm (Esposito et al., 2012). They typically cause mild infections involving the upper or lower respiratory tract, gastrointestinal tract, or conjunctiva (Esposito et al., 2012; Lynch et al., 2011). Dhurandhar et al. (2000) found that chicken and mice infected with adenovirus 36 showed a sharp increase in body weight due to substantial fat accumulation, whereas there was no significant variation in the body weight of animals inoculated with an avian adenovirus. The authors reported that 3 male marmosets inoculated with adenovirus 36 showed a threefold gain in body weight, greater fat gain, and lower serum cholesterol levels after 28 weeks compared to the baseline levels of 3 uninfected controls.

Effect of corticosterone and glucose on adenovirus and obesity

In a rodent model, adenovirus 36 decreases hypothalamic mono-amine levels and is associated with a decrease in corticosterone secretion (Pasarica et al., 2006), which impairs fatty acid metabolism (Gabbert et al., 2010). Corticosterone is suggested to prevent fat deposition by decreasing glucose transport into adipocytes and reduced levels of corticosterone prevent lipolysis (Pasarica et al., 2006). Esposito et al. (2012) also reported decreases in the secretion of corticosterone, which plays a major role in fat metabolism because it is required for the mobilization of glycerol from adipose tissue. Thus, lower circulating corticosterone levels in adenovirus 36-infected animals may contribute to their adiposity by reducing lipolysis and to increased insulin sensitivity by promoting glucose transport in adipocytes (Pasarica et al., 2006). Tsatsanis et al. (2010) also reported that lower circulating corticosterone levels in adenovirus 36-infected animal models may promote glucose transport in adipocytes and contribute to their adiposity independently from the amount of calories consumed (Esposito et al., 2012). In another study, adenovirus 36 was also found to increase glucose uptake in human skeletal muscle cells based on increases in gene expression and subsequent GLUT1/GLUT4 protein abundance, independent of insulin signaling (Wang et al., 2008). These findings indicate that adenovirus 36 may enhance insulin sensitivity in addition to having a proadipogenic effect (Pasarica et al., 2006).

Effect of adipocyte differentiation and leptin on adenovirus and obesity

In vitro studies have shown that adenovirus 36 infection accelerates the differentiation of preadipocytes to adipocytes in 3T3-L1 cells and human preadipocytes (Na and Nam, 2012; Vangipuram et al., 2004). The studies by Gabbert et al. (2010) and Vangipuram et al. (2004) suggest that adenovirus 36 enhances adipocyte differentiation, resulting in increased body fat through a peripheral pathway in preadipocyte 3T3-L1 cells. Rathod et al. (2009) also reported that adenovirus 36 significantly increased lipid accumulation in 3T3-L1 cells. Increases in the weight of reproductive fat pads and an inflammatory state that is maintained by macrophages are induced by an increase in monocyte chemoattractant protein-1 (MCP-1) levels (Na and Nam, 2012). Adenovirus 36 infection induces obesity through inflammation, and MCP-1 may be a key regulator of adenovirus 36-induced obesity in adenovirus 36-infected mice (Na and Nam, 2012). Thus, adenovirus 36 could cause chronic inflammation by increasing the levels of MCP-1 by activating nuclear factor κB (NF-κB), inducing the infiltration of macrophages into adipocytes, and altering lipid metabolism (Na and Nam, 2012). One potential link between obesity and immune responses is leptin, which plays a role in many diverse physiological processes but is primarily involved in energy homeostasis and satiety (Gale et al., 2004). Mancuso (2013) reported that leptin promotes Th1 cytokine production, elaboration of proinflammatory lipid mediators, and immune cell survival. Leptin expression and secretion are inhibited in cells infected

with adenovirus 36. Relative hypoleptinemia may contribute to increased preadipocyte differentiation and lipid accumulation in adenovirus 36-infected cells (Trovato et al., 2012). Vangipuram et al. (2006) reported that adenovirus 36 infection suppressed leptin mRNA levels in 3T3-L1 cells and increased glucose uptake, indicating that adenovirus 36 infection directly inhibits leptin gene transcription. The mechanisms underlying leptin modulation and glucose metabolism by adenovirus 36 still remain unclear. However, increased glucose uptake by adenovirus 36-infected adipocytes may contribute to increased lipid accumulation (Vangipuram et al., 2006). Moreover, the attenuation of leptin production in adenovirus 36-infected animals may also lead to increased adiposity through increased food intake, decreased energy expenditure, or both (Orci et al., 2004). Leptin stimulates lipolysis, inhibits the expression of genes involved in lipid synthesis, such as fatty acid synthase, and upregulates adipocyte genes involved in lipid oxidation (Vangipuram et al., 2006). Furthermore, leptin levels strongly correlate with the amount of lipid and its release is proportional to adipocyte volume (Zhang et al., 2008). Thus, the inhibition of leptin gene expression by adenovirus infection may increase lipid accumulation and obesity prevalence.

Pasarica et al. (2008) reported that human cells infected with adenovirus 36 showed greater differentiation and higher levels of lipid accumulation than noninfected control cells. The authors also demonstrated that norepinephrine levels in the paraventricular nucleus of the brain are significantly lower in adenovirus 36-infected rats than in healthy controls (Pasarica et al., 2006). The brain neurotransmitters, serotonin and norepinephrine, play an important role in the central nervous control of energy balance and are involved in symptomatology-related obesity and depression (Hainer et al., 2006). In general, endogenous norepinephrine inhibits the control of food intake. Norepinephrine released from sympathetic nerve terminals can both enhance and inhibit adaptive and innate immune cells (Kohm and Sanders, 2001). Therefore, a decrease in norepinephrine levels due to adenovirus may decrease immunity and increase food intake.

Adenovirus infection may increase appetite and food intake by decreasing norepinephrine levels and leptin, thereby increasing obesity prevalence; that is, prevention of viral infection can reduce obesity prevalence. The primary mechanisms for the effects of adenovirus infection on obesity are shown in Fig. 1.

Although many studies have shown that adenovirus is closely related with obesity prevalence, Goossens et al. (2011) reported that adenovirus does not directly cause increases in body mass index (BMI) and obesity in humans in Western Europe. The authors concluded that, at least in the Netherlands and Belgium, there were no significant correlations between adenovirus seropositivity and BMI, indicating that adenovirus infection is not always accompanied by obesity and that the evidence for and mechanisms underlying the relationship between adenovirus and obesity are unclear. Atkinson (2011) suggested that the differences between the study by Goossens et al. and previous studies may be due to issues with the assays used. For example, repeated freezing and thawing of human serum samples leads to decreases in antibody titers. There are approximately 50 types of human adenoviruses but their adipogenic potential is largely unknown (Vangipuram et al., 2004). Therefore, more research and epidemiological investigations are required in the future.

Influenza virus and obesity

The Center for Disease Control and Prevention has suggested that obese individuals are at an increased risk of morbidity and mortality from the pandemic influenza H1N1 strain (Karlsson and Beck, 2010). Louie et al. (2011) also reported that obese individuals infected with
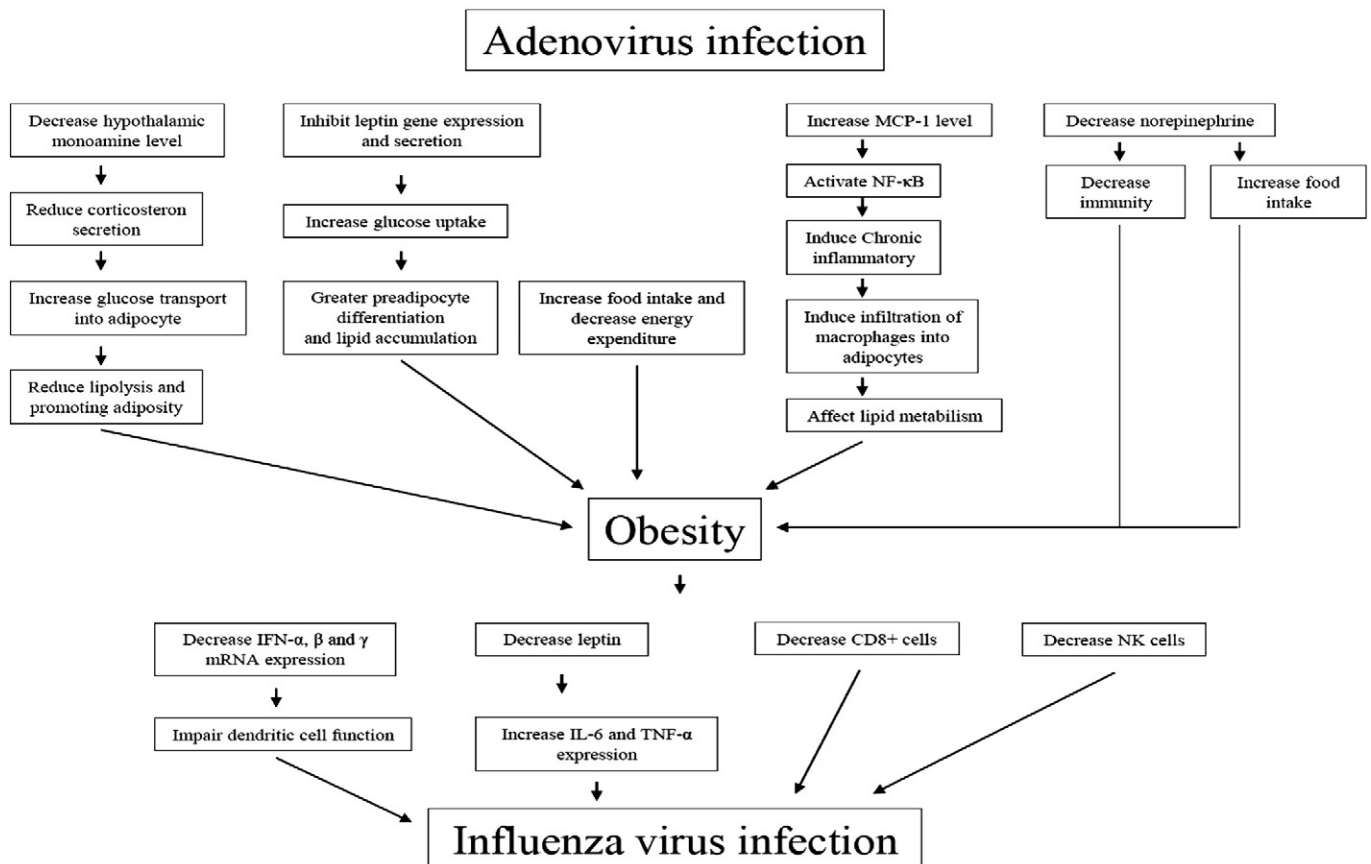

Fig. 1. Primary mechanisms for the effects of adenovirus and influenza virus infection on obesity.

the 2009 H1N1 virus were more likely to die once hospitalized (Louie et al., 2011). In addition, case patients with BMI ≥ 45 kg/m^2 had a 4.2-fold increased odds of dying with 34% case fatality (Louie et al., 2011).

Effect of immune cytokines and influenza virus and obesity

Adipose tissue not only is an energy store but also functions as an endocrine organ. Immune-related proteins produced by adipocytes include adipsin, acylation stimulation protein, adipocyte complement-related protein, TNF-α, and leptin (Martí et al., 2001). These immune cytokines may influence viral infection and obesity prevalence. Smith et al. (2007) found a significant decrease in the mRNA expression of IFN-α/β as well as an increase and delay in the expression of proinflammatory cytokines and chemokines in the lungs of influenza-infected, diet-induced obese mice. The authors (Smith et al., 2009) also reported that the decreased production of IFN-γ by memory T-cells during secondary infection in diet-induced obese mice may be due to the impairment of dendritic cell function. A similar study showed that the dendritic cell steady-state number and functionality decrease in genetically obese mice; in addition, the NK cell population diminishes in number and their level of function decreases (Karlsson and Beck, 2010). Therefore, impairment of dendritic cell functions in obese individuals may make them more susceptible to influenza virus infection. Mancuso (2013) also reported that pulmonary IFN-β and pro-inflammatory cytokine production in diet-induced obese mice was lower than that in lean control animals. Moreover, obese mice exhibited a decrease in type I IFNs (IFN-α and IFN-β); a delay in the expression of IL-6 and TNF-α, which eventually increased to levels greater than those observed in lean animals; and impaired NK cell cytotoxicity (Mancuso, 2013). Therefore, influenza virus infection could be influenced by decreases in IFN expression, impaired NK cell cytotoxicity, and increases in IL-6 and TNF-α expression in obese subjects.

Effect of CD8 + T-cells and NK cells and influenza virus and obesity

CD8 + T-cells play an important role in influenza infection in obesity. Obese subjects appear to have decreased CD8 + T-cell populations and increased or decreased numbers of CD4 + T-cells compared to those of lean controls (O'Rourke et al., 2005). Moreover, genetically obese animals have been reported to exhibit marked thymic atrophy as well as diminished splenic and circulating T-cell populations (Karlsson et al., 2010). Sherian et al. (2012) were the first to report that influenza vaccine antibody levels decline significantly and CD8 + T-cell responses are defective in obese individuals compared to individuals with healthy weight. Karlsson et al. (2010) also demonstrated that diet-induced 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. They observed that diet-induced obese mice exhibited a decrease in IFN-γ mRNA expression in the lungs as well as a decreased percentage and overall number of influenza-specific effector memory T-cells producing IFN-γ postsecondary challenge. In general, CD8 + T-cells kill virus-infected cells by releasing perforin and granzyme B and inhibiting viral replication by releasing IFN-γ (Sheridan et al., 2012). Therefore, modulation of IFN-γ and CD8 + T-cells by obesity may be closely related to influenza virus infection. Akiyama et al. (2011) reported that NK cell levels were significantly lower in obese subjects than in lean controls and animal models. In diet-induced obese mice with H1N1 influenza challenge, the production of IFN-γ and the number of influenza-specific memory T-cells significantly reduced and 25% of the mice died, compared to 0% mortality in control mice. O'Shea et al. (2010) also reported that obese individuals have decreased circulating NK cell populations with diminished activity. Moreover, high-fat dietary intake and diet-induced obesity in mice and rats result in decreased NK cell number and function (Li et al., 2005).

Thus, decreasing the IFN-α/β/γ, CD8 + T-cells, and NK cells in obese individuals may increase influenza virus infection. Thus, we assume that influenza virus infection is increased in obese individuals and is associated with the levels of IFN-α/β/γ, impaired function of NK cells, and a reduction in the number of influenza specific CD8 + T-cells.

Effect of leptin and influenza virus and obesity

Leptin, a 16-kDa peptide derived mainly from adipocytes, functions primarily in the hypothalamus as an anorexigenic signal to decrease food intake and increase energy expenditure (Friedman and Jürgens, 2000). Thus, leptin plays an important role in obesity prevalence and may be related to influenza virus infection. In terms of infectious disease, the general consensus is that leptin exerts a proinflammatory role, while serving in a protective capacity against infection (Karlsson and Beck, 2010). Friedman et al. (2000) also reported that leptin induces an acute-phase shift toward a Th1 cytokine-production profile, which is necessary for recovery from influenza infection. Leptin signaling is important for virtually all parts of the innate immune response, including the expression of antiviral cytokines (IFN-α/β), proinflammatory IL-6, and TNF-α and the activation and stimulation of monocytes, dendritic cells, and macrophages (Mattioli et al., 2005). Smith et al. (2007) found that leptin concentrations in lean mice transiently increased during influenza infection, whereas leptin decreased significantly during infection in the serum of obese mice, impairing the innate immune responses (Smith et al., 2007). Karlsson et al. (2010) suggested that leptin resistance in obese mice may contribute to the reduced protective capacity of the memory response to secondary influenza infection. Leptin has been shown to play a pivotal role in the modulation of immune function and decreasing leptin levels may impair the immune response. Thus, decreasing the levels of leptin in obese subjects may increase the susceptibility to influenza virus infection. In this regard, the relationship between influenza virus and obesity could be summarized by the following features: decreased memory T-cell functionality and IFN-α, IFN-β, and IFN-γ mRNA expression, increasing viral titer and infiltration, and impairment of dendritic cell function. Moreover, leptin reduction by obesity may play an important role in the upregulation of proinflammatory cytokine secretion, thereby increasing the susceptibility to influenza virus infection. Thus, prevention of obesity will be an excellent approach for reducing influenza virus infection.

Conclusion

There appears to be a different causal relationship between adenovirus and influenza infection with obesity. Adenovirus infection can cause obesity, whereas obesity can be a risk factor for increased influenza virus infection and an increased risk of morbidity and mortality. We also could not find a relationship between adenovirus and influenza virus infections in obesity models. The prevalence of obesity in individuals with adenovirus infections may be due to an increase in glucose uptake and reduction in lipolysis due to increases in corticosterone secretion. Adenovirus infections may increase appetite and food intake by decreasing norepinephrine and leptin levels and cause immune dysfunction. The relationship between influenza virus and obesity could be summarized by the following features: decreased memory T-cell functionality and IFN-α, IFN-β, and IFN-γ mRNA expression, increasing viral titer and infiltration, and impairment of dendritic cell function in obesity. Moreover, leptin resistance may play an important role in obesity prevalence, thereby increasing influenza infection. In this review, we have provided several, but not all, pieces of evidence for the relationship between virus infections and obesity. Therefore, additional research or epidemiological investigations are required for the development of antiviral and antiobesity therapy.

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