

## Viruses as an Etiology of Obesity

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Obesity is a serious chronic disease that has numerous etiologies. The prevalence of obesity has increased dramatically since about 1980 in the United States and worldwide in both developed and developing countries. This rapid spread is compatible with an infectious origin. This review discusses the 5 animal viruses and 3 human viruses that have been shown to cause obesity and examines the evidence to date for virus-induced obesity. The obesogenic animal viruses include canine distemper virus, Rous-associated virus type 7, Borna disease virus, scrapie agent, and SMAM-1. The first 4 viruses attack the central nervous system to produce obesity. SMAM-1, an avian adenovirus from India, acts directly on adipocytes and is the only animal virus that is associated with human obesity. The 3 human adenoviruses, adenovirus (Ad) 36, Ad-37, and Ad-5, that are associated with obesity also affect adipocytes directly. These viruses stimulate enzymes and transcription factors that cause accumulation of triglycerides and differentiation of preadipocytes into mature adipocytes. Ad-5 and Ad-37 have been shown to cause obesity in animals. Ad-36 has been studied the most and is the only human adenovirus to date that has been linked with human obesity. Ad-36 causes obesity in chickens, mice, rats, and monkeys and was present in 30% of obese humans and 11% of nonobese humans. In twins discordant for infection with Ad-36, the infected twins were heavier and fatter than their cotwins. The growing body of evidence demonstrating that viruses produce human obesity supports the concept that at least some of the worldwide epidemic of obesity in the past 25 years is due to viral infections.

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Ad = adenovirus; BDV = Borna disease virus; BMI = body mass index; CNS = central nervous system

Obesity is a chronic disease of multiple etiologies, including genetic, metabolic, environmental, social, and other factors.<sup>1</sup> According to the National Health and Nutrition Evaluation Survey, the prevalence of obesity in the United States was about 13% in 1960 and increased to about 15% by 1980, an increase of 1.5% of the population.<sup>2,3</sup> However, in the next 20-year period from 1980 to 2000, the prevalence of obesity increased at a 10-fold higher rate and by 2000 was about 31% of the US population.<sup>2,5</sup> The prevalence of obesity doubled in adults and tripled in children during that 20-year period.<sup>3,4</sup> The increase in the prevalence of obesity occurred not only in the

United States but also worldwide, starting at about the same time.<sup>5</sup> The World Health Organization proclaimed a global epidemic of obesity and appointed an International Obesity Task Force to deal with this problem.<sup>5,6</sup>

Many attempts have been made to explain this epidemic of obesity, and some creative explanations have been advanced.<sup>6,7</sup> Clearly, simple behavioral changes in diet and lifestyle are not entirely sufficient to explain the epidemic.<sup>1,7</sup> One potential explanation of the "epidemic" is that truly it is an epidemic due to infectious causes, specifically virus-induced obesity, at least in part. This review discusses published evidence for viruses that cause obesity, focusing first on animal viruses in animal models, then on human viruses in animal models and in humans.

### ANIMAL VIRUSES AS AN ETIOLOGY OF OBESITY

Viral-induced obesity is not a new concept (Table 1). The first report of obesity due to a virus was published in 1982,<sup>8</sup> and 4 other animal viruses have been reported since then.<sup>9-12</sup>

#### CANINE DISTEMPER VIRUS

In the first report, Lyons et al<sup>8</sup> described a syndrome of massive obesity in about one-fourth of Swiss albino mice that were survivors of infection with canine distemper virus. Canine distemper virus invades the central nervous system (CNS) and replicates in neurons and glial cells of the white matter.<sup>13</sup> It causes encephalomyelitis, the most common cause of death.<sup>14</sup> The article by Lyons et al<sup>8</sup> showed only hypertrophic, hyperplastic obesity with no obvious CNS damage. Subsequent articles demonstrated that the hypothalamus in the infected mice had altered neurochemistry and subtle anatomical damage.<sup>15-23</sup> It is well known that damage to the hypothalamus can cause obesity with elevated levels of serum cholesterol and triglycerides.<sup>24</sup> Canine distemper virus is not thought to be a human pathogen. However, human measles virus is closely related to canine distemper virus and belongs to the same family of Paramyxoviridae viruses.<sup>8</sup>

#### ROUS-ASSOCIATED VIRUS TYPE 7

Carter et al<sup>25</sup> reported that Rous-associated virus type 7 could induce obesity in chickens. It causes a syndrome of obesity in chickens that is associated with stunting of

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growth, hypertriglyceridemia, and hypercholesterolemia. Some of the chickens had serum triglycerides levels higher than 2000 mg/dL, and 1 chicken had serum triglycerides higher than 14,000 mg/dL. Infected chickens develop enlarged fatty livers, anemia, and immunosuppression. Obesity developed despite similar levels of food intake, and lower thyroid hormone levels were detected. The authors attributed the obesity to hypothyroidism, but it is likely that CNS damage was responsible.

#### BORNA DISEASE VIRUS

Borna disease virus (BDV) is an enveloped, negative-stranded RNA virus with a genomic size of approximately 9 kilobase with replication and transcription in the nucleus of the host cell.<sup>26-28</sup> Narayan et al<sup>10</sup> and Gosztonyi et al<sup>29,30</sup> reported that BDV produces obesity in rats. It causes a lymphomonocytic inflammation of the septum, hippocampus, amygdala, and ventromedial hypothalamus<sup>31</sup> and persists in the nervous system; thus, the mechanism of obesity is probably CNS damage.<sup>31-33</sup> Hyperplasia of pancreatic islets, elevated serum glucose levels, and hypertriglyceridemia are evident but are likely manifestations of obesity, rather than a direct virus effect. Interestingly, the age of the animals at the time of inoculation plays a role in the development of obesity.<sup>29</sup> Rats infected as newborns with BDV show a progressive neurological disease within 12 to 16 months and become obese later. In contrast, weanling or adult rats inoculated with BDV develop acute encephalitis and many die within 1 to 4 months. Some of the rats that survive the infection develop marked obesity.<sup>30</sup>

Borna disease virus has been found in a wide variety of animals,<sup>32,33</sup> and there is evidence that it affects humans. de la Torre<sup>34</sup> found BDV-specific antigen and BDV-RNA with hippocampal sclerosis and astrocytosis in 4 human brains at autopsy. Borna disease virus has been associated with schizophrenia and depression in humans,<sup>35,36</sup> and these cases were responsive to amantadine, an antiviral drug.<sup>37,38</sup> Evidence shows that BDV causes behavioral disorders in a variety of animals, particularly horses, and cycles of elevated antibodies to BDV have correlated with cyclic psychiatric disorders in humans.<sup>39,40</sup> As yet, no evidence exists for a contribution of BDV to human obesity, but additional study is needed.

#### SCRAPIE AGENT

Scrapie is a fatal neurodegenerative disease classified as a transmissible spongiform encephalopathy.<sup>41</sup> Natural infection occurs in sheep and goats, but in the laboratory, hamsters, mice, rats, voles, gerbils, mink, cattle, and some species of monkeys have been infected with scrapie by inoculation of the agent.<sup>41</sup> The 3 main theories on the nature

TABLE 1. Animal and Human Viruses That Produce Obesity

Virus	Year reported
Animal	
Canine distemper virus	1982
Rous-associated virus type 7	1983
Borna disease virus	1983
Scrapie agent	1987
SMAM-1 avian adenovirus	1990
Human	
Adenovirus 36	2000
Adenovirus 37	2002
Adenovirus 5	2005

of the scrapie agent are that it is a prion, a virus with unusual characteristics, or a virino, a very small piece of DNA that acts like a virus.<sup>41</sup> Currently, no evidence exists that scrapie infects humans, but clearly some of the transmissible spongiform encephalopathies do, such as Creutzfeldt-Jakob disease and kuru. Kim et al<sup>11</sup> reported that the ME-7 strain of scrapie produced obesity in mice, but other scrapie strains did not. Kim et al<sup>42</sup> suggested that the hypothalamic-pituitary-adrenal axis was necessary for the development of obesity by showing that removal of the adrenal gland prevented obesity. However, several models of obesity in mice are prevented by adrenalectomy; thus, an intact hypothalamic-pituitary-adrenal axis is necessary for obesity, but it does not seem likely that it plays a primary role in the etiology of obesity due to scrapie. Diabetes is associated with scrapie but is due not only to the obesity but also to damage of the pancreas by the scrapie agent.<sup>43-52</sup>

#### SMAM-1

In the mid-1970s, an increased death rate was noted in commercial chicken farms in India. Ajinkya<sup>53</sup> found that an avian adenovirus was responsible and named it SMAM-1. SMAM-1 is associated with decreased immune function and an increased accumulation of body fat in infected chickens. Dhurandhar et al<sup>12,54</sup> studied SMAM-1 and noted that it was highly infectious and caused obesity without an increase in food intake in these growing chickens. Uninoculated chickens in the same room with chickens inoculated with SMAM-1 developed the obesity syndrome, presumably due to airborne virus particles.<sup>54</sup> In addition, serum lipids of the infected chickens had a paradoxical decrease with SMAM-1 infection compared to controls, and livers of infected chickens were large and filled with triglycerides.<sup>12,54</sup> Body fat increased but body weight did not always increase compared to controls, suggesting that fat was preferentially stored, even at the expense of lean body mass.<sup>12,54</sup> SMAM-1 was the first virus, animal or human, associated with human obesity.<sup>55</sup>

TABLE 2. Increase in Percent Visceral Fat and Prevalence of Obesity in Animals Infected With Human Adenovirus 36 vs Controls

	Visceral fat, % increase	Obesity prevalence, infected vs control (%)
Chickens		
Experiment 1	100	69
Experiment 2	129	64
Experiment 3	72	70
Mice	67	60
Marmosets	66	100

### HUMAN VIRUSES ASSOCIATED WITH OBESITY IN ANIMALS

Because SMAM-1 is an animal adenovirus associated with obesity in humans,<sup>55</sup> the possibility was raised that human adenoviruses might also be associated with obesity. Of the 51 different human adenoviruses, 3 to date have been shown to cause obesity in animal models, whereas 2 have not.<sup>56-63</sup> Adenovirus (Ad) 36 and Ad-37 were shown to cause obesity in chickens, but Ad-2 and Ad-31 were not.<sup>57-59</sup> So et al<sup>62</sup> showed that Ad-5 produces obesity in mice. Ad-36 has been shown to cause obesity in infected chickens, mice, hamsters, rats, and monkeys.<sup>57-60,63,64</sup> Ad-36 is the only virus that has been shown to be associated with human obesity.<sup>61,65</sup> In the initial experiments with Ad-36 in chickens, Ad-2 and avian adenovirus chick embryo lethal orphan virus did not cause obesity.<sup>57</sup> Thus, production of obesity is a not a characteristic of all adenoviruses or human adenoviruses.

#### HUMAN AD-36

Ad-36 was the first human adenovirus to be tested. Ad-36 was first isolated in 1978 and reported in 1980 to the American Type Culture Collection.<sup>66</sup> Although the virus could have been present for a long time previously, the timing of this isolation is interesting because it occurred just before the worldwide epidemic of obesity. Dhurandhar et al<sup>57-59</sup> reported that in both chickens and mice after Ad-36 inoculation, body fat increased, visceral fat increased disproportionately to body fat, and serum lipids were paradoxically lower despite the obesity. Table 2 summarizes the experiments in chickens and mice and demonstrates that about 60% to 70% of chickens and mice that were infected with Ad-36 became obese, either by body fat or by visceral fat criteria.<sup>57-59</sup> The brains of the infected animals were evaluated, and no anatomic lesions were seen.<sup>57,59,60</sup> Pasarica et al<sup>64</sup> infected rats, monitored them for 30 weeks, and noted that body weight and body fat were increased significantly in the infected rats compared with controls.

To determine the degree of infectivity and potential hazards of blood transfusion, Dhurandhar et al<sup>59</sup> transfused 200  $\mu$ L of blood from infected chickens into uninfected chickens. The transfused chickens developed full-blown Ad-36 infection and obesity, illustrating that the virus could be transmitted from blood. In addition, the study fulfilled Koch's postulate that obesity could be transmitted from infected animals to uninfected animals.

Two experiments have been performed in nonhuman primates.<sup>60</sup> Serum samples from the University of Wisconsin Primate Center serum bank of the Non-Human Primate Aging Study were tested every 6 months for 7 years for the presence of antibodies to Ad-36 using a serum neutralization assay.<sup>60</sup> There was no cross-reactivity of Ad-36 antibodies with other adenoviruses; thus, the test is specific for Ad-36.<sup>57,67</sup> Of the 15 rhesus monkeys at baseline, 7 already had been infected, and the remaining 8 became infected during the course of the study. The extended period during which the monkeys became infected suggested they were exposed on several occasions to Ad-36 from human handlers, but it is possible that the infection was present in the monkey colony and gradually infected all the monkeys in this experiment. The change in weight in the 18 months before the first positive serum neutralization assay was compared to the increase in body weight after the animals became positive. Body weight increased by about 15%, and serum cholesterol decreased about 25% in the 18 months after the first positive Ad-36 assay.<sup>60</sup>

Two groups of marmosets were used for the second experiment on nonhuman primates.<sup>60</sup> Three marmosets were inoculated intranasally with Ad-36 and followed up for 7 months along with 3 uninfected control marmosets. At baseline, body weight, body fat by stable isotope dilution, and serum cholesterol level were measured. As noted in Table 2, all the infected marmosets gained adiposity. Body weight increased by about 4-fold more in the infected vs uninfected monkeys (41 vs 11 g), and visceral fat increased by 66% in the infected monkeys. In contrast, serum cholesterol decreased by 34 mg/dL in the infected monkeys vs controls despite the gain in weight and fat in the infected monkeys. Virus could be isolated from the feces of infected monkeys for 2 months but not thereafter. However, at 7 months, viral DNA was identified in brain, lung, liver, muscle, and adipose tissue of infected monkeys by polymerase chain reaction assay. These data illustrate that Ad-36 spread throughout the cells of the body at the time of initial viremia, but the infectious virus had disappeared by about 2 months.

Of perhaps great importance, the serum neutralization assay for Ad-36 antibodies was positive in only 2 of the 3 infected monkeys. However, the third monkey had Ad-36 DNA in all the tissues tested after 7 months. This finding

suggests that not every infected individual will have a positive serum antibody assay; thus, this test may underestimate the prevalence of infection.

#### HUMAN Ad-37

Whigham et al<sup>63</sup> evaluated Ad-37, Ad-31, and Ad-2 in chickens. Ad-2 and Ad-31 did not cause an increased fat deposition, but Ad-37 increased body fat by 111% and visceral fat by 262% compared to the controls during a period of 3.5 weeks. Food intake was not different in any of the virus groups; thus, obesity developed in the Ad-37 chickens apparently because of changes in energy expenditure.

In contrast to Ad-36, which caused a decrease in serum cholesterol levels in chickens and other animal models, Ad-37 caused an increase by 25% compared to baseline.<sup>63</sup> Levels of serum triglycerides decreased by 51% with Ad-37; thus, Ad-36 and Ad-37 both act to cause a paradoxical decrease in triglycerides despite increased obesity. Serum lipids were not changed with Ad-2 and Ad-31.

#### HUMAN Ad-5

So et al<sup>62</sup> inoculated mice intraperitoneally with Ad-5 and found that body fat increased by almost 300% without increased food intake. Body fat was measured with proton magnetic resonance spectroscopy rather than with chemical analysis. Evaluation of the liver showed no fatty deposition by this method. Unfortunately, serum lipids were not measured. The authors speculated that inflammation due to the virus might stimulate production of peroxisome proliferator-activated receptor- $\gamma$ , which would increase differentiation of new fat cells and lead to obesity.

### VIRUSES ASSOCIATED WITH OBESITY IN HUMANS

Information on virus-induced obesity in humans is limited. Dhurandhar et al<sup>55</sup> showed that SMAM-1 was associated with obesity in obese humans in Bombay, India. In clinical studies in humans with Ad-36, Atkinson et al<sup>61</sup> demonstrated a correlation of increased body weight in a general population and in twins.

#### SMAM-1

Dhurandhar et al<sup>55</sup> assayed 52 obese humans in Bombay for antibodies to SMAM-1 using an agar-gel-precipitation test. About 20% (10/52) of the study participants had antibodies to SMAM-1. These participants were heavier ( $95.1 \pm 2.1$  kg vs  $80.1 \pm 0.6$  kg;  $P < .02$ ) and had a higher body mass index ( $35.3 \pm 1.5$  kg/m<sup>2</sup> vs  $30.7 \pm 0.6$  kg/m<sup>2</sup>;  $P < .001$ ) compared with the antibody-negative group. Levels of serum cholesterol and triglycerides were significantly lower in partici-

TABLE 3. Adenovirus 36 Antibody Status and Body Mass Index (BMI) in Study Participants From 3 US Cities\*

Study participants	BMI (kg/m <sup>2</sup> )	
	Antibody positive	Antibody negative
Obese ( $\geq 30$ kg/m <sup>2</sup> )	47.7 $\pm$ 15.6	41.8 $\pm$ 10.6 <sup>†</sup>
Nonobese ( $< 30$ kg/m <sup>2</sup> )	26.3 $\pm$ 4.2	23.9 $\pm$ 3.8 <sup>‡</sup>
Combined	44.9 $\pm$ 16.3	35.8 $\pm$ 12.3 <sup>‡</sup>

\*Values are mean  $\pm$  SD.

<sup>†</sup> $P < .0001$ .

<sup>‡</sup> $P < .02$ .

pants who had antibodies to SMAM-1: cholesterol was 33 mg/dL (16%;  $P < .02$ ) lower, and triglycerides were 88 mg/dL (41%;  $P < .001$ ) lower. No other information is available regarding the mechanisms of SMAM-1 obesity in humans or the prevalence of SMAM-1 antibodies in the general population, but the authors concluded that this avian adenovirus may infect humans.

#### HUMAN Ad-36

Atkinson et al<sup>61</sup> measured antibodies to Ad-36 in 502 individuals of varying body weights, both obese and nonobese, from 3 cities in the United States: New York City, Madison, WI, and Naples, FL. Ad-36 antibodies were found in 30% of obese individuals and 11% of lean individuals. There were no significant differences in age or sex between antibody-positive and antibody-negative individuals. A highly significant difference in body mass index (BMI) was noted between antibody-positive and antibody-negative individuals in the population as a whole and between individuals whether they were obese or nonobese (Table 3). In the whole population, antibody-positive individuals were 9 BMI units heavier than antibody-negative individuals. Smaller but still significant differences were present in the obese and nonobese subgroups.<sup>61</sup> Levels of serum cholesterol and triglycerides were paradoxically significantly lower in Ad-36 antibody-positive individuals than in the antibody-negative individuals. Serum cholesterol levels were 34 mg/dL lower in infected individuals, similar to the findings in the marmosets that were prospectively infected (as previously mentioned); levels of triglycerides were 39 mg/dL lower in antibody-positive individuals.<sup>61</sup>

Atkinson et al<sup>61</sup> also measured antibodies to Ad-2, Ad-31, and Ad-37 and found no difference in BMI or serum lipids between antibody-positive and antibody-negative persons. However, only 5 persons were positive for Ad-37. Greenway<sup>65</sup> concluded that Ad-36 was the only human adenovirus that has been correlated with human obesity since Ad-37 infection is so infrequent and Ad-5 has not been tested.

A study of 89 twin pairs from New York City was conducted.<sup>61</sup> Because twins tend to be similar in many characteristics, including body weight, twin pairs discordant for Ad-36 antibodies were studied. Antibody-positive twins were slightly, but significantly, heavier and fatter than their antibody-negative cotwins; the BMI was  $24.5 \pm 5.2$  vs  $23.1 \pm 4.5$  kg/m<sup>2</sup> ( $P < .03$ ) and percent body fat was  $29.6 \pm 9.5\%$  vs  $27.5 \pm 9.9\%$  ( $P < .04$ ), respectively, in the antibody-positive vs antibody-negative twins. The twin pairs were significantly younger than the individuals in the aforementioned general population study. There were no differences in BMI or percent body fat in cotwins discordant for antibodies to Ad-2, Ad-31, or Ad-37.<sup>61</sup> In contrast to the other experiments mentioned previously, no differences were noted in serum lipids in the discordant twin pairs.

### MECHANISMS OF VIRUS-INDUCED OBESITY

Most of the animal viruses noted previously cause obesity by damaging the CNS. In the initial experiments of Ad-36 infection by Dhurandhar et al,<sup>57</sup> no anatomical lesions were found in the CNS. However, Ad-36 DNA measured by polymerase chain reaction was consistently found in adipose tissue of multiple animal models, as mentioned previously.<sup>57-60</sup> Fat pads from infected animals were larger than similar pads from uninfected animals, and they contained both an increase in fat cell size and an increase in fat cell number,<sup>57-60</sup> suggesting a peripheral action of Ad-36 directly on fat cells.

Dhurandhar et al<sup>57</sup> and Vangipuram et al<sup>68,69</sup> evaluated the effects of Ad-36 in murine preadipocytes (3T3-L1 cells) *in vitro*. Ad-36 stimulated a rapid differentiation response in preadipocytes with significantly faster appearance of enzymes of fat storage and differentiation factors, accumulation of triglycerides, and differentiation to mature adipocytes.<sup>57,63,64,68-70</sup> Ad-2 did not have this effect on preadipocytes *in vitro*.<sup>68</sup> Whigham et al<sup>63</sup> analyzed the effects of Ad-2, Ad-31, Ad-36, and Ad-37 and confirmed that Ad-2 has no effect on preadipocyte differentiation but that the other 3 viruses enhance differentiation. They concluded that *in vitro* testing cannot be used to define which human adenoviruses will cause obesity because Ad-31 infection did not produce obesity in experimental animals but was positive *in vitro*.

Vangipuram et al<sup>68</sup> found that glycerol-3-phosphate dehydrogenase, a marker for adipocyte differentiation, increased much faster in infected than in uninfected preadipocytes using both 3T3-L1 cells and human preadipocytes. Oil red-O staining showed that triglycerides accumulated much faster in both cell types. This study confirmed that Ad-36 affected human preadipo-

cytes in the same manner as it did animal cells, giving support to the hypothesis that Ad-36 causes obesity in humans.

Vangipuram et al<sup>69</sup> also evaluated leptin expression and insulin sensitivity in 3T3-L1 cells and found that Ad-9, Ad-36, and Ad-37 suppressed the expression of leptin messenger RNA by about half. Insulin sensitivity, as measured by glucose uptake, was enhanced by these 3 viruses in rat primary adipocytes.<sup>69</sup> Adipose tissue of Ad-36-infected rats was excised and cultured.<sup>69</sup> Leptin messenger RNA expression was lower by 2- to 5-fold, and expression of acetyl-coenzyme A carboxylase 1 and fatty acid synthase, key enzymes for *de novo* lipogenesis, were significantly increased in the infected rats compared to weight- and adiposity-matched controls. The authors found that Ad-9 enhanced fat accumulation in cells in tissue culture, but Ad-9 has not been studied in *in vivo* experiments.

Pasarica et al<sup>64</sup> infected rats and noted that fasting insulin was lower and insulin sensitivity higher in the infected rats. Norepinephrine levels in the paraventricular nucleus and serum corticosterone were both significantly lower in infected vs control rats. The authors suggested that, in addition to peripheral effects of Ad-36 in adipose tissue, changes in the CNS may be involved in the etiology of Ad-36-induced obesity.

Rathod et al<sup>70</sup> showed that Ad-36 gene expression in 3T3-L1 cells was attenuated by cidofovir, an antiadenoviral agent. Specifically, expression of the early gene 4 open reading frame 1 could be decreased with use of cidofovir. Rogers et al<sup>71</sup> have shown that this gene is critical for differentiation of preadipocytes and accumulation of triglycerides.

### CONCLUSION

Numerous published articles validate the concept of obesity due to virus infections. Five animal viruses and 3 human viruses have been shown to cause obesity in animals, and 1 human adenovirus, Ad-36, has been correlated with obesity in humans. The data from twins in which one member of the twin pair is infected and the other is not infected provide perhaps the best evidence that Ad-36 causes obesity in humans. The infected twins were heavier and fatter than the uninfected cotwins. The mechanisms of Ad-36-induced obesity have been uncovered, and it appears that Ad-36 has a direct effect on adipocytes to turn on the enzymes of fat accumulation and recruitment of new adipocytes. In total, these data strongly support the concept that at least part of the epidemic of obesity that has occurred since about 1980 is due to viral infections.

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