Review Article

ASSOCIATION OF HUMAN ADENOVIRUS (AD-36) WITH OBESITY IN HUMAN AND ANIMALS: A REVIEW

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ABSTRACT

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. It is defined by body mass index (BMI) and further evaluated in terms of fat distribution via the waist–hip ratio and total cardiovascular risk factors. Human adenovirus 36 (Ad-36) is one of 52 types of adenoviruses known to infect humans. The American Diabetes Association (ADA) says that Ad-36 is, "one of a family of about 50 viruses that cause colds, upper respiratory infections, gastrointestinal problems, and eye inflammations," and that researchers have identified Ad-36 as a causative factor in developing obesity in humans and other animals. Ad-36 was first identified in 1978. Since that time, initial studies showed that the virus caused obesity in chickens, mice, and rats. Eventually, research with primates exposed to the virus showed that they became obese also. This article presents a brief review of association of Human adenovirus (Ad-36) with obesity. Ad-36, a human adenovirus, that produce a syndrome of visceral obesity, with paradoxically decreased serum cholesterol and triglycerides in chickens and mice.

Keywords: Human adenovirus, Ad- 36, Adenovirus serotype 36, HAdV-36, adenoviruses, obesity.

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems[1]. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight (pre-obese) if their BMI is between 25 kg/m^2 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2. Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, breathing difficulties during sleep, certain types of cancer, and osteoarthritis. Evidence to support the view that some obese people eat little yet gain weight due to a slow metabolism is limited; on average obese people have a greater energy expenditure than their thin counterparts due to the energy required to maintain an increased body mass[1] . Dieting and physical exercise are the mainstays of treatment for obesity. To supplement this, or in case of failure, anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption.

In severe cases, surgery is performed or an intragastric balloon is placed to reduce stomach volume and/or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food. Obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and authorities view it as one of the most serious public health problems of the 21st century. Obesity is stigmatized in much of the modern world (particularly in the Western), though it was widely perceived as a symbol of wealth and fertility at other times in history, and still is in some parts of the world[2].

Description about human adenovirus-36 (AD-36):

Human adenovirus 36 (HAdV-36) or Ad-36 or Adv36 is one of 52 types of adenoviruses known to infect humans. AD-36 was first isolated in 1978 from the faeces of a girl suffering from diabetes and enteritis[3], and has long been recognized as a cause of respiratory and eye infections in humans. It was first shown to be associated with obesity in chickens by Dr. Nikhil Dhurandhar[4, 5]. There has been a positive correlation between body fat and the presence of AD-36 antibodies in the blood[6]. Previous research showed that chicken or mice injected with similar types of viruses show a statistically significant weight gain. To date, AD-36 is the only human adenovirus that has been linked with human obesity, present in 30% of obese humans and 11% of non obese humans. In addition, a study of obese Americans indicates that about 30% of the obese individuals and only 5% of non-obese individuals have antibodies to Ad-36. Another study determined that children with the virus averaged 52 pounds heavier than those with no signs of it and obese children with the virus averaged 35 pounds heavier than obese children with no trace of the virus. AD-36 also causes obesity in chickens, mice, rats, and monkeys[7].

AD-36 infection can induce cellular differentiation of 3T3-L1 preadipocytes and stem cells derived from human adipose tissue[8]. Besides obesity, another interesting symptom of the virus is that animals that are infected have what are called "paradoxically low" levels of both cholesterol and triglycerides, which in medical terms are often referred to as "serum lipids." The paradox arises because high levels of both cholesterol and triglycerides have been traditionally associated with obesity. The reaction from the medical community to the

news that the virus caused obesity in primates was primarily to ignore it or to claim that it would not affect humans in the same way. This was surprising since primate studies have traditionally been a major indicator of how a disease or condition would impact humans. Further research found that around 30% of obese people are infected with the Ad-36 virus, compared to only 11% of those at a healthy weight, according to the ADA article. That article also pointed out that animals infected with the virus gained weight even though their diet remained the same. This clearly demonstrates that obesity can still occur without ingestion of excess calories, and that the virus may change the way infected animals process food and store fat.

Association of the human adenovirus-36 (AD-36) with obesity:

Although obesity is recognized as a disease of multiple etiologies, microbial infection as an etiological factor has received consideration relatively recently[9, 10].

Not all obesity can be explained by viral infections. However, if certain pathogens promote human obesity, recognizing their role is the first important step in addressing the infection and its pathogenesis. An accurate understanding of the varied etiological factors of obesity may lead to cause-specific treatments and, consequentially, its successful management. Seven viruses, a scrapie agent, a parasite, and gut microflora have been reported to cause obesity in animal models[11].Whether these pathogens cause obesity in human's remains to be determined. Ethical reasons preclude experimental infection of humans. Determination of the causative role of a virus in humans will have to depend on indirect evidence, such as elucidating the mechanism of adipogenic action in tissue culture and animal models and applying it to observations in humans. So far, adenoviruses are the only adipogenic viruses linked with human obesity and therefore form prime targets for determining the role of adipogenic viruses in human obesity. The human adenovirus-36 (Ad-36) was first described in 1980, about the time that the prevalence of obesity began to increase[12]. Prevalence of obesity increased by 30% between 1980 and 1990 and by 61% between 1990 and 2000 with no indication that this increase is lessening[13]. The reason for this epidemic increase in obesity is not clear, but dietary changes, such as an increase in dietary fructose derived from corn syrup[14], increased food intake[15], and decreased physical activity have all been suggested as potentially playing a role. Infectious agents such as viruses are another possible contributing factor[16]. Support for Ad-36 being a contributor to the obesity epidemic has been accumulating over several years. Ad-36 has been shown to cause obesity in chickens, mice, and nonhuman primates[17].

Obese humans have a higher prevalence of serum neutralizing antibodies to Ad-36 (30%) than lean humans (11%), and the antibody-positive obese or non obese subjects are heavier compared with their antibody negative counterparts. Similarly, when human twins are discordant for antibodies to Ad-36 antibodies, the antibody-positive twin has a higher body mass index (24.5 ± 5.2 vs. 23.1 ± 4.5 kg/m^2, $P < 0.03$)[18] .Obese humans positive for antibodies to SMAM-1, an adipogenic avian virus[19], are heavier compared with their seronegative obese counterparts. However, because avian viruses are not thought to infect humans, this observation has been interpreted as a cross-reaction to a human virus that is antigenically similar[20]. The mechanism by which Ad-36 causes obesity has been explored. Ad-36 accelerates differentiation of preadipocytes to adipocytes in 3T3-L1 cells, and this has been confirmed in human preadipocytes, as well[21]. When the open reading frame E4orf1 from the Ad-36 virus was inserted into 3T3-L1 cells, C/EBP-β, PPARγ-2, and glycerol 3-phosphate dehydrogenase were all stimulated compared with the control 3T3-L1 cells, suggesting that the viral gene E4orf1 is responsible for the stimulation of adipocyte differentiation[22]. If Ad-36 is responsible for a significant portion of human obesity, the logical therapeutic intervention would be to develop a vaccine to prevent future infections. If a vaccine were to be developed, one would want to ensure that all the serotypes of human adenoviruses responsible for human obesity were covered in the vaccine. If one could predict the potential of an adenovirus to cause human obesity by using an in vitro assay or even by animal testing, screening of the ~50 human adenoviruses might be accelerated, shortening the time required for vaccine formulation. In addition to Ad-37 causing obesity in chickens, Ad-5 was recently shown to cause obesity in mice[23]. Adenovirus Ad-2 does not cause adiposity in animals and does not enhance differentiation of 3T3-L1 or human preadipocytes.

Ad-37, Ad-31, and Ad-5 have not been tested for increased differentiation in human adipocytes. The experience with Ad-36 suggests that 3T3-L1 cells function as a good model for defining the mechanisms by which human adenoviruses induce obesity in humans, if the virus in question stimulates adipocyte differentiation in human cells. Thus it is possible that human adipocyte differentiation may be a viable in vitro assay to screen for human adenoviruses capable of inducing obesity in humans. Antibody testing in humans suggests that the development of obesity in chickens is not an effective screening tool to identify human adenoviruses capable of causing obesity in humans. The prevalence of antibodies to Ad-2 was not different in 145 obese human subjects compared with 52 lean controls. The prevalence of antibodies to Ad-31 in 152 obese human subjects was not different compared with 49 lean controls. Because there were only 5 of 198 people positive for the Ad-37 virus, its role in the etiology of human obesity seems remote, despite its demonstrated ability to cause obesity in chickens.

This may be due to a lower potential for this virus to cause infection. Infectivity of Ad-36 was 100% in studies

when chickens were inoculated with this virus, because all animals developed antibodies to Ad-36 but only 71% of the chickens inoculated with Ad-37 developed antibodies. At this point, it appears that Ad-36 is the only human adenovirus associated with human obesity based on human antibody titers. If virus infections are partially responsible for the human obesity epidemic, it will be important to define all the adenovirus serotypes responsible in formulating a vaccine. Screening of large populations for the differential prevalence of antibodies to all 50 or more human adenoviruses to define those associated with human obesity is a daunting task. Clearly, an in vitro assay would make the screening process much more efficient. Obesity has multiple etiologies, but infectious agents have been consistently overlooked as a possible origin of human obesity. Three animal viruses have been reported to cause obesity in nonprimate species, but have not been implicated in initiating or maintaining obesity in humans[24, 25]. The reaction from the medical community to the news that the virus caused obesity in primates was primarily to ignore it or to claim that it would not affect humans in the same way. This was surprising since primate studies have traditionally been a major indicator of how a disease or condition would impact humans. Further research found that around 30% of obese people are infected with the Ad-36 virus, compared to only 11% of those at a healthy weight, according to the ADA article. That article also pointed out that animals infected with the virus gained weight even though their diet remained the same. This clearly demonstrates that obesity can still occur without ingestion of excess calories, and that the virus may change the way infected animals process food and store fat.

In summary, evidence is accumulating that Ad-36 plays a role in human obesity by stimulation of adipocyte differentiation. Other adenoviruses cause obesity in animals and stimulate 3T3-L1 preadipocyte differentiation but neither of these findings correlates with the antibody prevalence in obese and lean humans shown with Ad-36.

Therefore, human antibody prevalence in obese and lean human populations appears to be the only reliable method to screen adenoviruses for their potential to cause obesity in humans at the present time an in vitro assay that correlates with human antibody prevalence would accelerate screening of adenovirus serotypes for their potential to induce human obesity. Identifying such an in vitro assay will be important to efficient vaccine development. Obesity is an incredibly complex disease with wide variety of causes. All causes should be investigated without bias and moral judgment based in misinformation and pre-existing biases. No matter the cause of obesity for any particular person, diet and behaviour can be modified so that the effects of the disease can be minimized or ended. Proper nutrition, physical activity, and a diet low in added sugars (such as high fructose corn syrup) and saturated fats (particularly hydrogenated oils) will do a great deal toward maintaining or achieving a healthy body.

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