Infectobesity: a New Area for Microbiological and Virological Research

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Obesity is connected with numerous diseases, such as type 2 diabetes, atherosclerosis, cancer, and nervous system dysfunctions. Obesity is affected by genetic, environmental, and cultural factors. However, numerous studies indicate that several pathogens might cause obesity. This review discusses recent data and the characteristics of pathogens that are implicated in obesity. In particular, human adenovirus 36 (Ad36) is the most clearly implicated virus in human obesity. It was recently shown that obese groups from the USA, Korea, and Italy have a higher prevalence of serum antibodies against Ad36. The mechanisms of Ad36-induced obesity remain unclear. However, glucose uptake and inflammation are possible mechanisms of Ad36-induced obesity. Overall, this new understanding of causes of obesity has developed into the concept of 'infectobesity' and the possibility of developing a 'vaccine' or 'therapeutic agents' for obesity.

Key Words: Infectobesity, Adenovirus 36, Obesity

Overweight and obesity are leading risk factors affecting mortality worldwide. At least 2.8 million adults die every year as a result of being overweight or obese. According to global estimates from the WHO, there were 1.5 billion overweight adults in 2008. Over 200 million men and 300 million women were considered to be obese (Fig. 1A and 1B). Thus, more than one in ten of the world's adult population was obese. Close to 35 million overweight children live in developing countries and eight million in developed countries, which means that overweight children are a problem in all countries. Overweight and obesity also account for 44% of the diabetes burden, 23% of the ischemic heart disease burden, and between 7% and 41% of certain cancer burdens. Recently, the obesity rate among Koreans has increased drastically (Fig. 1C). In 1995, 11.7% of women and 18% of men were considered to be obese. However, 29.4% of women and 32.6% of men were considered obese in 2001 and the obese ratio recently increased further. There was also a noticeable increase in the ratio of obese children and adolescents (1).

The costs of treating obesity and obesity-related metabolic disease account for 40% of total health expenditure in the USA and this recent trend is dramatically increasing (2). The social and economic cost of obesity therapy is more than 1 billion dollar and diabetes treatments account for 19.2% of the national medical insurance premium in Korea (3). Thus, obesity-related diseases are a severe loss to the national economy.

There are many causes for obesity, such as genetics, medical problems, or psychiatric illness. Simply put, obesity is a result of an energy imbalance, where the energy intake is greater than energy expenditure (4) and excess energy accumulates in adipose tissue. Increasing rates of obesity at the societal level are attributed to easy access to a palatable diet, increased dependence on cars, and mechanized manufacturing. However, the recent increase in obesity might be
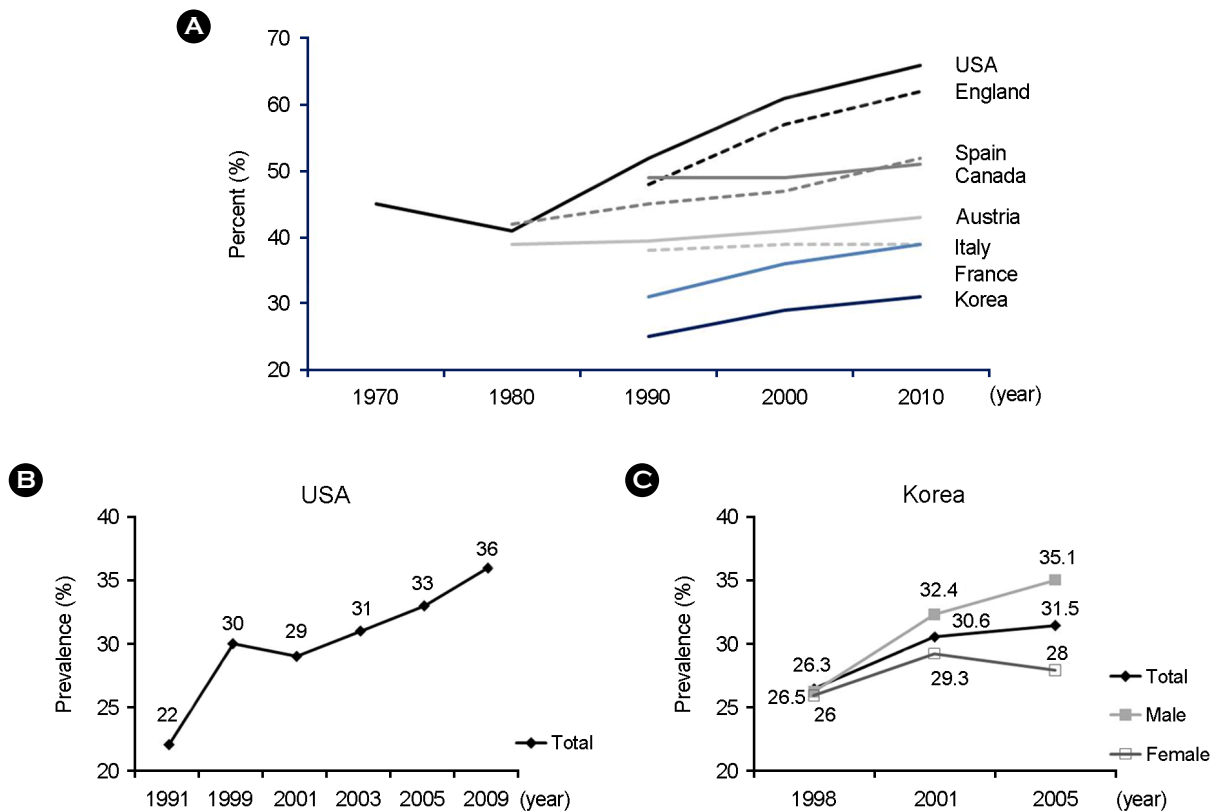
Figure 1. Increasing ratios of obese population are appeared all over the world as Europe, Asia, and USA. (A) Global obesity percentage. Obesity prevalence in the USA (B) and Korea (C). (1, 2)

affected by other contributory factors, including insufficient sleep, endocrine disruption, use of medications that cause weight gain, proportional increases in ethnic and age groups that tend to be heavier, pregnancy at a later age, epigenetic risk factors passed on generationally, natural selection for higher body mass index (BMI), and assortative mating leading to an increased concentration of obesity risk factors (5).

Many factors are implicated in obesity, but one important factor is often overlooked. Several pathogens are known to be related to obesity. Approximately 30 years ago, several pathogenic microbes and viruses were shown to cause weight gain. Thus, the term 'infectobesity' was coined to describe the theory that obesity in some individuals was caused by pathogens (6~8). The pathogens led to greater weight gain and fat storage. The concept of infectobesity might lead to changes in many areas, such as medical treatments and societal views of those who are significantly

obese. Therefore, a better understanding of pathogens as etiological factors is required for medical treatment of obesity. The following report reviews the role of several pathogens known to be involved in obesity.

Summary of pathogens connected to obesity

This section discusses several pathogens that are connected with obesity. They are summarized in Table 1 (6~11). Several microbial agents, such as *Chlamydia pneumoniae* and gut microbiota, are known to have effects on animal obesity. Several viruses also induce obesity in animals, such as mice, rats, and chickens. These pathogens lead to increased body weight, fat mass, and hyperlipidemia in animal subjects. Associations between pathogens and human obesity are unknown or unclear. However, Ad36 is known to be related to obesity in both animals and humans.

Table 1. Pathogens correlated with obesity (Reference 6~11)

	Year first reported	Animal model	Effect on Body weight	Effect on biochemical parameters	Association with human obesity
Scrapie	1968	Mice	↑Body weight due to fat accumulation	Brain function alteration	Not reported
Chlamydia pneumoniae	2000	Human	↑Significantly higher BMI	Association with coronary heart disease	Partially yes
Gut microbiota	2004	Mice	↑whole body fat 57% ↑epidemal fat 69%	Increased insulin resistance and glucose	Yes
CDV	1982	Mice	↑number and size of fat cell	Alters hypothalamic integrity	Not reported
RAV-7	1983	Embryos-chicken line	↑obesity ↑hyperlipidemia	Hepatomegaly, anemia and immune suppression	No
SMAM-1	1990	Chicken	↑excessive visceral fat	Enlarged liver, kidney, hepatic fatty infiltration and congestion	Partially yes
BDV	1991	Rats	↑serum glucose ↑triglyceride	Inflammation lesions and viral replication in hypothalamus	Not reported
Ad-37	2002	Chicken	↑obesity	Differentiated 3T3-L1 preadipocytes	No
Ad-5	2002	Mice	↑Obesity	Important role of predispositioin to obesity	Not reported
Ad-36	2000	Chicken, Mice, Rhesus and marmoset monkeys, Rats	↑body weight ↑visceral fat ↑epidermal fat ↑inguinal fat	E4 orf-1 Increase adipose tissue, low levels of serum cholesterol and TG	Strongly yes Epidemiological data

1. Scrapie

Scrapie is a degenerative disease that influences the nervous systems of sheep and goats (12). Prion proteins enter through the intestines or a skin wound. These proteins gradually accumulate in the body, particularly in the nerve cells. Prions cause normal proteins to fold into the wrong shape, which leads to abnormal behavior and motor dysfunction. Some scrapie strains also lead to obesity in infected mice and hamsters (13). Mice infected with scrapie strains show a significant increase in body weight. The ME7 and 22L scrapie strains are linked to hypothalamus-induced obesity (14). It was also found that different brain regions showed reduced glucose tolerance after scrapie infection (15). However, there are no reports showing that scrapie is related to human obesity.

2. *Chlamydia pneumoniae*

Chlamydia pneumoniae is a species of *Chlamydophila*

bacteria that infects humans, which is a major cause of pneumonia (16). It is a small bacterium (0.2 to 1.0 micrometer) that experiences several transformations during its life cycle and it exists as an elementary body in the host. The elementary body is transmitted from an infected person to the lungs of an uninfected person in small droplets. Once in the lungs, the elementary body is taken up by phagocytosis into a cellular endosome. Bacterial infection causes several illnesses, such as arthritis, myocarditis, meningoencephalitis, and Guillain-Barré syndrome. Interestingly, it was reported that *Chlamydia pneumoniae* infection is associated with human obesity (17). People with persistent *C. pneumoniae* antibodies have a significantly higher BMI and chronic inflammation (18). This shows that bacterial infection is related to BMI in humans. However, the mechanism leading to obesity in humans is unknown.

3. Gut microbiota

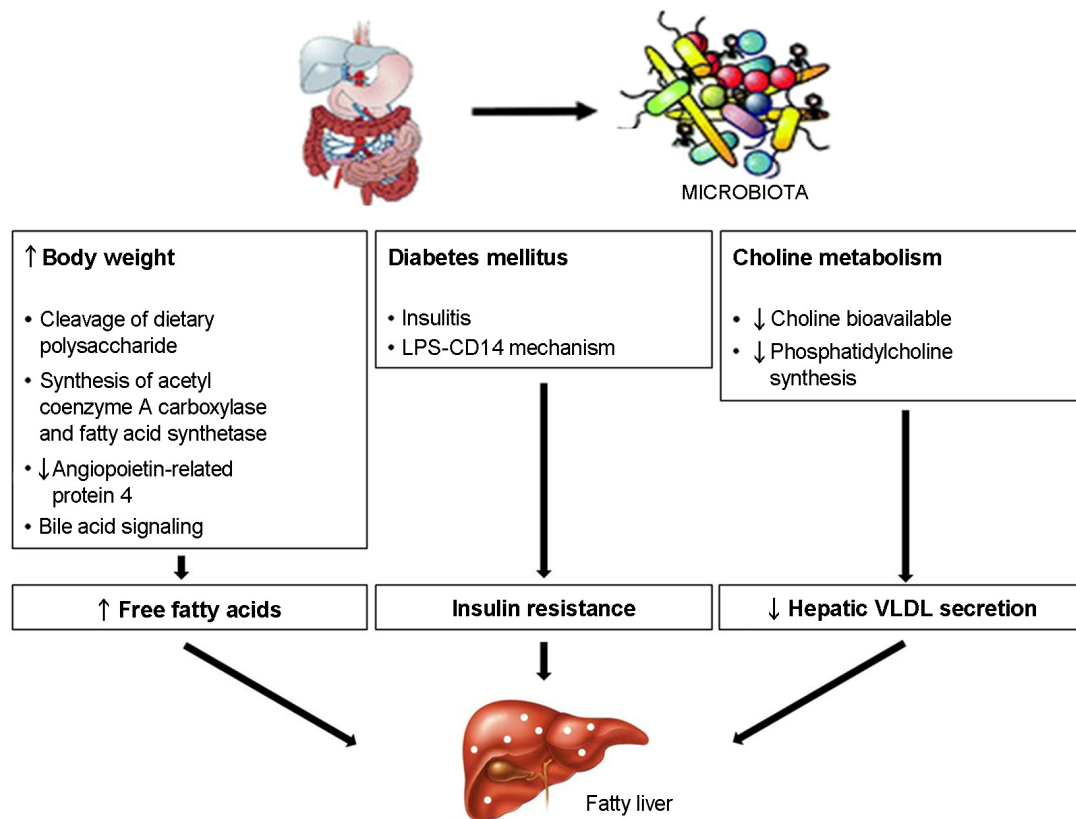The gut microbiota consists of microorganisms that live

Figure 2. Effects of gut microbiota (25). Infection with gut microbiota increases body weight and free fatty acid in serum. It induces insulin resistance and reduces hepatic VLDL secretion. Therefore gut microbiota effects fatty liver production.

in the digestive tracts and the diversity of species found in populations varies widely among individuals (19). Bacteria perform many functions in the human gut, including, digestion of energy substrates, repressing the growth of harmful microorganisms, and training the immune system to respond to pathogens (20). The gut microbiota may play a role in the development of obesity via nutrient acquisition and energy regulation (21, 22). The bacterial flora of obese mice and humans contain fewer *Bacteroides* and more *Firmicutes* than lean groups (23, 24). Gut microbiota can increase body weight and free fatty acids, and induce insulin resistance (Fig. 2) (25). Therefore, the interaction among microorganisms in the gut has a significant role in host energy homeostasis.

4. Canine distemper virus (CDV)

CDV affects animals, such as dogs and other carnivorous mammals (26). CDV is a single-stranded RNA virus in the paramyxovirus family. This virus tends to infect lymphoid, epithelial, and nervous tissues, leading to respiratory, gastrointestinal, and central nervous system disease. In 1982, CDV was found to induce obesity in infected mice and to increase the number and size of fat cells (27). CDV-infected mice also showed higher insulin levels compared with the control group. CDV infection also reduced circulating catecholamine levels and hypothalamic damage (28). The hypothalamus plays an important role in stimulating blood-borne hormones, such as leptin, ghrelin, angiotensin, insulin, and cytokines. Leptin can be secreted into the blood stream and enters the brain. Leptin has an effect on adipose tissue mass (29). However, it is not known whether CDV affects human obesity.

5. Rous-associated virus-7 (RAV-7)

RAV-7 belongs to subgroup C of the five subgroups of the avian retrovirus, based on its envelope glycoproteins

Table 2. Subgroups of human adenoviruses (Reference 39)

Subgroup (species)	Hemagglutination groups	Serotypes	Percentage of GC in DNA	Disease
A	IV (little or no agglutination)	12, 18, 31	48~49	Meningoencephalitis
B	I (complete agglutination of monkey erythrocytes)	3, 7, 11, 14, 16, 21, 34, 35, 50	50~52	Acute respiratory disease
C	III (partial agglutination of rat erythrocytes)	1, 2, 5, 6	57~59	Acute febrile pharyngitis
D	II (complete agglutination of rat erythrocytes)	8, 9, 10, 13, 15, 17, 19, 20, 22~30, 32, 33, 36~39, 42~49, 51	57~61	Epidemic Keratoconjunctivitis
E	III	4	57~59	Pneumonia
F	III	40, 41	50~52	Gastoenteritis
G	–	52	55	Gastoenteritis

(30). The virus has been reported to cause obesity, hyperlipidemia, and hypercholesterolemia in chickens (30). Infected chickens developed fatty, yellow-colored livers, hepatomegaly, immune suppression, and striking hyperlipidemia (30). Serum triglyceride levels in infected chickens increased more than 17-fold compared with uninfected chickens (31). The virus induced pancreatic damage by histological changes, increased serum amylase levels, and reduced serum glucose and glucagon levels (31). The virus-induced syndrome explains the role of hypothyroidism in the development of RAV-7-induced adiposity. It is known that RAV-7 cannot infect humans.

6. SMAM-1

SMAM-1 is an avian adenovirus that is serologically similar to chick embryo lethal orphan virus (8). The SMAM-1 virus is probably transmitted via aerosols. This makes it very contagious. Infected chickens have excessive visceral fat, an enlarged liver and kidneys, and hepatic fatty infiltration (8, 32). SMAM-1-infected groups had lower levels of serum lipid and lower body weight, but a higher amount of visceral fat. Only recently was it shown that SMAM-1 has no influence on human health. However, 20% of obese humans possess antibodies to SMAM-1 along with lower serum triglycerides and cholesterol (32). Further research is required to confirm whether SMAM-1 infections are linked to human obesity.

7. Borna disease virus (BDV)

BDV is a neurotropic virus and a member of the Bornaviridae family, which are single negative-stranded RNA viruses (33). The virus is mainly found as a causative factor of borna disease in horses, birds, rodents, and primates (34). BDV may also play a role in human neurological and psychiatric conditions. BDV mostly targets the nervous system, but it replicates in other organs, such as the bladder, pancreas, lungs, liver, and spleen. The virus causes 'Induced Obesity Syndrome' in rats, and increased serum glucose and triglyceride levels (35). It can also induce lympho-monocytic inflammation in the hypothalamus and hyperplasia in the pancreatic islets (36). BDV infection appears to cause obesity by neuroendocrine dysregulation. Thus, BDV-induced inflammatory lesions may adversely affect specific brain regions that are involved in body weight regulation and food intake (37). However, there is insufficient evidence that BDV causes obesity in humans. Thus, we need more detailed research to confirm BDV-induced obesity in humans and animals.

8. Human adenovirus

Human adenoviruses are classified into seven subgroups (A-G) and 56 serotypes (Table 2) (38). They are double-stranded DNA viruses with an icosahedral structure (Fig. 3). Adenoviruses are transmitted via respiratory, droplet, venereal, and fecal-oral routes (8). Adenoviruses often affect

the upper respiratory track, but they can produce serious symptoms elsewhere, such as enteritis and conjunctivitis (Table 2) (39).

1) Human adenovirus type 36 (Ad36)

Ad36 belongs to subgroup D of the 56 adenoviruses (38). It is known that Ad36 infection is related to obesity in both animals and humans. The virus infection significantly increased weight gain in chickens (40), mice (41), and primates (42). There is also a positive correlation between

Figure 3. Structure of human adenovirus 36 (38). Human adenovirus 36 is nonenveloped isosahedral structure and medium size (90~100 nm). Purified virion fraction is symmetry (rotational axes) and the architecture of the hexon-penton-relation becomes apparent.

body fat and the prevalence of the Ad36 antibodies in human serum (43). We consider that Ad36 is the only virus to cause human obesity, although there is a possibility that SMAM-1 might be linked, because Ad36 is the only virus that was detected by mass surveillance of human populations. Therefore, we have included more detail on this virus in a separate part of this review.

2) Human adenovirus type 37 (Ad37)

Ad37 infection increases obesity in chickens and the virus also differentiates 3T3-L1 preadipocytes (44, 45). When chickens were infected with Ad36, the infectivity of the virus was 100%, but chickens with Ad37 infection showed only 71% infectivity. There was no correlation between Ad37 and human obesity. There were only five positive Ad37 results among 198 people (46). Therefore, Ad37 is related to obesity in animals, but the virus is not associated with human obesity.

3) Human adenovirus 5 (Ad5)

Ad5 belongs to subgroup C of the human adenoviruses and genetically modified forms of this virus are used as candidate vectors in gene therapy (47). Thus, it is important to determine whether Ad5 can induce obesity in humans (10). Ad5 infection was identified as causing obesity in mice (48). The percentage of adipose tissue in virus-infected mice significantly increased compared with the control
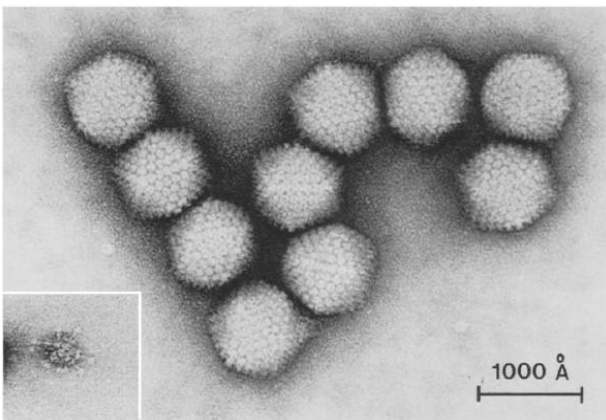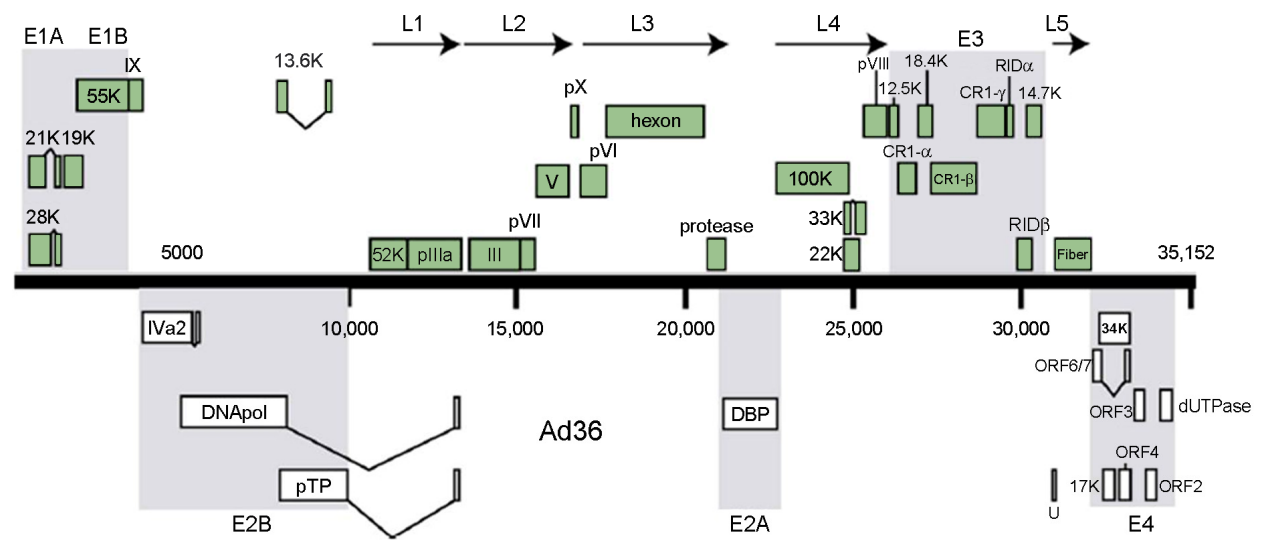

Figure 4. The structure of Ad36 (49). The genome length of Ad36 is 35,152 bp with the GC content at 57.2%. The organization of the 39 open reading frames (ORFs) was similar to that of other adenoviruses.

Table 3. Homology of amino acid sequences with Ad36 (Reference 49)

	Ad8	Ad9	Ad19	Ad22	Ad28	Ad37	Ad49	Ad53
Pentonbase	91.4	92.1	93.3	92.3	92.3	90.6	91.7	90.6
Hexon	91	90.5	90.1	91	90.5	90.7	91.8	91
CR1β	46.5	48.6	48.3	46	51	45.8	85	47.1
CR1γ	69.9	64.3	87	69	61	70.1	66.9	69.6
Fiber	69	64.3	62.4	68.7	65	62.4	66	63.5
ORF4	90.8	91.7	89.2	91	83.5	90	91.7	91.7
ORF3	88.9	88	88	86	87.2	88	88	88.9
ORF2	86.2	86.9	86.9	86	93.8	86.9	87.7	86.2
ORF1	84	92	47.2[a]	91.2	91.2	47.2[a]	91.2	84.8

[a] Shorter proteins due to frameshift

group. However, any correlation between Ad5 infection and human obesity is unknown.

Adenovirus 36

Ad36 was first isolated in 1978 from a six-year-old diabetic German girl (7). The Ad36 genome length is 35,152 bp and the organization of the 39 open reading frames (ORFs) of the virus is similar to mastadenoviruses (Fig. 4) (49). Ad36 differs antigenically from other adenoviruses and has no cross-reactivity with them, which is very important in the diagnosis of Ad36-specific antibody using serological methods, such as serum neutralization assays (43). The amino acid sequences of Ad36 are different from other adenoviruses (Table 3) (49). This low amino acid homology might account for the lack of serological cross-reactivity.

In support of the infectobesity concept, a link between the Ad36 virus and obesity was established in several animals and humans 30 years ago. Ad36 infection increases body weight, fat deposition, and insulin sensitivity, but decreases cholesterol and triglyceride levels (40, 42, 43). In contrast, several studies found no relationship between Ad36 seropositivity and human obesity, including, Dutch, Belgian (50), and USA military studies (51). All epidemiological studies of Ad36 are cross-sectional studies. Thus, there are fundamental limitations on interpreting this epidemiological data. There is a strong need for longitudinal research studies

and a diverse range of epidemiological surveys of the human population to confirm whether Ad36 is related to human obesity.

1. Animal studies

Animal research into Ad36 was performed using diverse species. Chickens and mice were first infected with Ad36 in 2000 (40, 45). Food intake of the Ad36-infected chicken and noninfected chickens was equal, but the body weight and total body fat of Ad36-infected chickens increased. At 13 weeks post infection, all chickens possessed antibodies to Ad36 and their visceral fat increased by 74% (40). Ad36-infected mice also showed increased body weight, total body fat, and visceral fat. However, the serum cholesterol and triglyceride levels of the Ad36-infected group decreased in chicken and mice (52). We found that Ad36-infected mice (Balb/c and C57BL mice) showed no increase in total body weight, but there was an increase in the weight of their reproductive fat pads (53). Rhesus and marmoset monkeys infected with Ad36 in 2002 showed increased body weight, but decreased cholesterol, 18 months after infection (42). Furthermore, Ad36-infected rats showed increased body weight and visceral fat, but decreased insulin, HOMA index, and cholesterol (53). Animal research of Ad36 infection confirmed that the virus can induce adiposity, but paradoxically it increases insulin sensitivity.

Table 4. Prevalence of Ad36 in human populations

Children (%)		Obese	Overweight
	Korean cohort 1 (57)	30[a] (25/84)	
	Korean cohort 2 (56)	29 (74/259)	
	US cohort 1 (54)	22 (15/67)	
Adults (%)			
	Korean cohort 3 (in press IJO)	30 (54/180)	40 (72/180)
	US cohort 2 (43)	30 (108/252)	
	US cohort 3 (51)	34 (68/104)	
	Europe cohort 1 (55)	65 (51/150)	
	Europe cohort 2 (50)	6 (28/509)	

[a] percentage (positive / total number)

2. Human studies

Surveillance of Ad36 prevalence in human populations was performed in several countries to test the relationship between Ad36 and human obesity (Table 4). In 2005, the prevalence of the Ad36 antibody was tested in obese and nonobese subjects in the USA (Florida, New York, Wisconsin) (43). This study found that 30% of obese subjects had Ad36-neutral antibodies, while 11% of nonobese subjects were identified as seropositive. The BMI of the Ad36 antibody-positive group was 44.9±16.3, whereas that of the Ad36 antibody-negative group was 35.8±12.3 (43). Ad36 infection was associated with an increase in the BMI of subjects, but the virus decreased serum cholesterol and fasting serum triglyceride levels. Therefore, the correlation between Ad36 infection and BMI was important from a human obesity perspective. Ad36 infection can increase body fat, but paradoxically it decreases serum lipid. Children in the USA also showed a relationship between Ad36 and obesity (54). It was found that 22% of obese children tested as seropositive. The BMI of the seropositive obese group was 36.4±5.9, whereas the BMI of the seronegative group was 31.8±4.4. Ad36 infection was closely connected with

human obesity in Italy (55); and 28% of obese and 13% of nonobese Korean schoolchildren were shown to be seropositive (56, 57). However, when we extended this study to Korean adults we determined Ad36 antibody positivity in 32% of nonobese subjects, 40% of overweight subjects, and 30% of obese subjects. Thus, there was no relationship between Ad36 seropositivity and obesity. However, the odds ratio of the overweight group was 2.03-fold higher compared with the normal group (in press, Int J Obes). Based on these data, it was concluded that Ad36 infection was significantly correlated with obesity in Korea. These research studies provide considerable data to support infectobesity, but some studies do not agree with the concept, such as the Dutch and Belgian epidemiological studies (50). Other research found no association between Ad36 infection and US military personnel that were forced to exercise regularly (51). These surveillance data suggest that adult lifestyle factors, such as diet and exercise, may have a significant influence on Ad36-induced obesity. However, more intensive epidemiological studies are required to confirm this.

3. The mechanism of Ad36-induced obesity

Molecular research into Ad36 is at an early stage. Mechanistic studies have approached the possible role of Ad36 from various perspectives. First, there was an attempt to identify a novel regulator of Ad36-induced obesity. The Ad36 E4 open reading frame 1 (orf-1) is an important viral gene with effects on proliferation and differentiation (58). The gene can regulate the adipogenic process and induce cellular signaling pathways. Ad36 E4 orf-1 was expressed in 3T3-L1 cells and human adipose-derived stem cells (hASCs) and the cells differentiated into adipocytes (adipogenesis) and accumulated lipid (increased glucose uptake) (44, 59). Furthermore, Ad36 E4 orf-1 increased the mRNA levels of C/EBPβ and PPARγ genes, which are relevant to adipogenesis, and upregulated cAMP activity. Adipogenesis and lipid accumulation decreased when Ad36 E4 orf-1 was knocked down by RNAi (58). Therefore, Ad36 E4 orf-1 could play an important role in inducing adipogenesis.
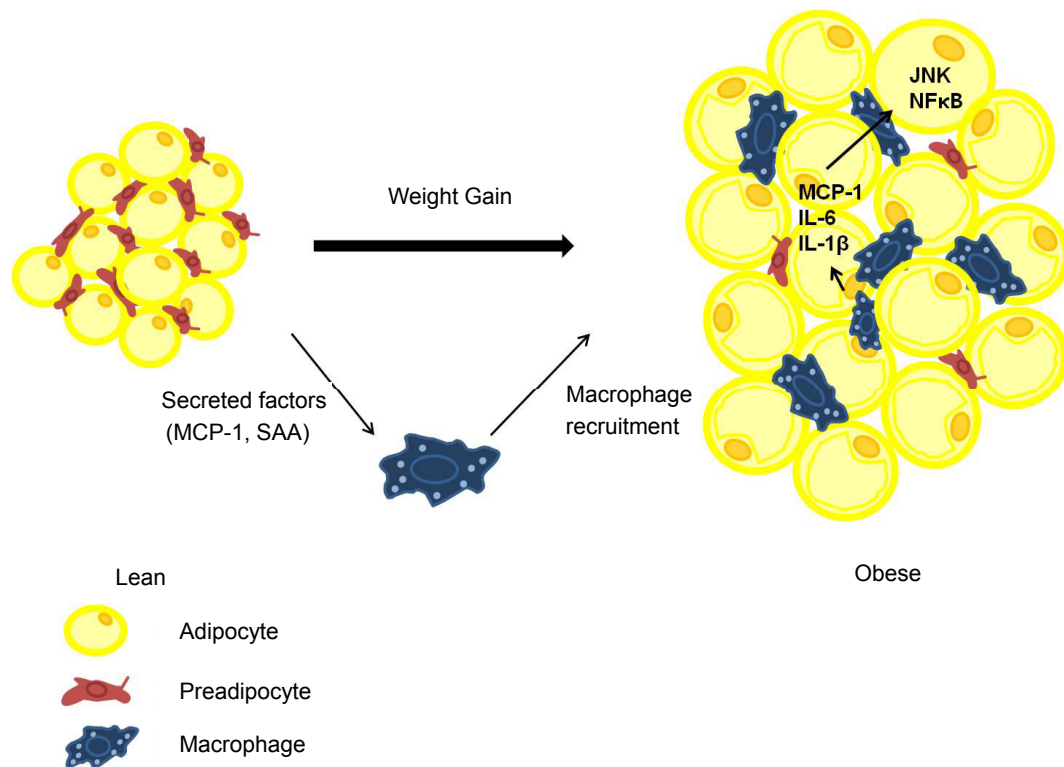
Figure 5. Inflammation state in obesity (63). When adipocytes undergo hypertrophy, releasing chemokines that induce recruitment M1-polarized macrophages increased MCP-1 and IL-6.

The insulin receptor substrate (IRS) is generally phosphorylated by insulin influx and activates phosphoinositide 3-kinase (PI3K). Increasing glucose transporter 4 (GLUT4) can regulate glucose uptake (60). The quantity of GLUT1 and GLUT4 is also regulated by insulin (61). This quantitative regulation of glucose transporters is influenced by the PKB/AKT signal via PI3K (62). Interestingly, Ad36 infection increased RAS, PI3K, and PKB/AKT signaling and the protein level of GLUT1. However, phosphorylation of IRS1/2 was decreased (59). Thus, Ad36 infection increased glucose uptake and augmented GLUT4 expression via RAS signaling, rather than via the phosphorylation of IRS.

The concept of Ad36 E4 orf-1 as a key regulator is interesting, but it cannot explain how acute Ad36 infection can lead to chronic obesity, because E4 orf-1 might disappear after viral infection. According to our data, active Ad36 virus particles disappeared less than two weeks after infection. However, infected mice showed an increase in the size of reproductive fat pads 90 days after infection. These data seem to be contradictory. Therefore, we need to focus on other possible mechanisms, such as the host response after viral infection (59, 60).

It is well established that chronic inflammation has an important role in maintaining obesity (Fig. 5). The number and size of adipocytes are maintained in the original condition. However, as obesity advances, proinflammatory cytokines and chemokines are secreted by augmented adipocytes (63~65). Immune cells and macrophages infiltrate the adipocytes and remodeling of adipose tissue occurs because of angiogenesis (66). The infiltrated macrophages secrete interleukin 6 (IL-6), IL-8, tumor necrosis factor-α (TNF-α), and monocyte chemoattractant protein-1 (MCP-1) (67, 68). Adipocytes lose homeostasis of the free fatty acid pathway during the inflammatory state. We studied the connection between Ad36 infection and inflammation based on the relationship between obesity and inflammation. Reproductive fat pads increased in size in C57BL/6 mice

90 days after Ad36 infection. Infiltrated M1 macrophages and proinflammatory cytokine, such as MCP-1 and TNF-α, were also upregulated in adipocytes. However, the size of reproductive fat pads did not increase in MCP-1 knockout mice after Ad36 infection. Proinflammatory cytokines were also decreased, despite the infection, and macrophages did not infiltrate adipocytes (Submitted for publication). Therefore, it is suggested that Ad36 infection can maintain the obesity state by promoting a chronic inflammatory condition.

Conclusion

Ad36 is generally known as a virus that induces obesity, but epidemiological and molecular studies to understand its mechanism are inadequate. Several studies support the infectobesity concept, but other studies are contradictory. Therefore, extensive epidemiological surveys and longitudinal section studies are needed to test the concept. Further research is required to determine how Ad36 infection promotes obesity by cellular mechanisms. These research studies might lead to new drugs and vaccines and provide a cure for Ad36-induced obesity. As far as we know, global infectobesity research is at an early stage. This may be a new research area for virologists.

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