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Infectobesity? Role of Ad-36 virus

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Abstract- Obesity is one of the greatest challenges of our time affecting vast majority of population. It is a serious chronic disease that has numerous etiologies. The Human Adenovirus-36 (Ad-36) was first described in 1980, about the time that the prevalence of obesity began to increase. Support for Ad-36 being a contributor to the obesity epidemic has been accumulating over several years and has been shown to cause obesity in chickens, mice and nonhuman primates.[1]The purpose of this study was to determine the prevalence of Ad-36 virus in obese and non-obese individuals.

Plasma titers of Ad-36 virus were evaluated in 20 obese and 21 non obese individuals. Blood samples were obtained from obese subjects with BMI 27-34 and also from non-obese controls with BMI <27. Ad-36 titers were estimated using Real-time PCR SYBR green I fluorescence assay. Statistically increased titers of Ad-36 were found in obese subjects when compared to those of non-obese controls ($p<0.001$). Thus, in our study, titers of Ad-36 virus are increased in obese individuals suggesting that this virus may play a role in etiology of obesity.

Index Terms- Ad-36 virus, body mass index, infectobesity, real time PCR

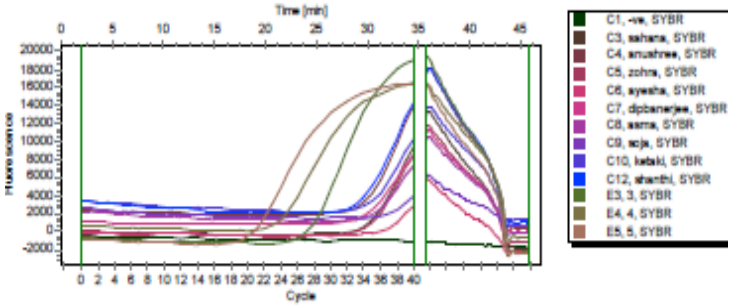
I. INTRODUCTION

Obesity is serious chronic multifactorial disease affecting mankind in epidemic proportions. Hence the term "globesity" defines its current situation.[2] Bariatrics is the branch of medicine that deals with the causes, prevention, and treatment of obesity. **Sclafani (1984)** classified the etiology of animal obesity into 9 groups, including obesity of neural, endocrine, pharmacological, nutritional, environmental, seasonal, genetic, idiopathic, and viral origin.[2]The rapid increase in obesity and the associated health care costs have prompted a search for better approaches for its prevention and management. Such efforts may be facilitated by better understanding the etiology of obesity.

Recently, viral infections have been recognized as possible cause of obesity.[3]So the term infectobesity can be used to describe the growing nature of it. To date, in animals six viruses and a scrapie agent have been shown to be associated with obesity.[4]Of the several etiological factors, infection, an unusual causative factor, has recently been receiving greater attention. Understanding contribution of various etiologic factors of obesity may lead to treatments directed specifically toward the cause, and consequently, its successful management.

II. MATERIALS AND METHODS

The present study was conducted on 20 obese (BMI- 27-34) and 21 non-obese individuals (BMI < 27) between age group 20-40. Patients were taken from outpatient department of our institute. Patients with long time medication, chronic debilitating diseases and endocrine disturbances were excluded from the study. Age and sex matched individuals served as controls. Ethical clearance for conducting study was obtained from the Institutional Ethical Clearance Committee. Weight in kilograms was measured using digital weighing machine and height was measured using height chart for both obese subjects and controls. Body mass index was calculated by formula weight in kilograms/ height in metres square. 5ml blood was collected from obese subjects and controls under aseptic conditions, stored in EDTA vials until dispatched to laboratory. Ad-36 viral load was estimated using real time PCR SYBR green 1 fluorescence assay.[5]



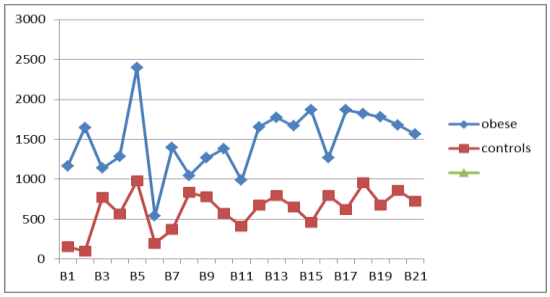
III. RESULTS

Analysis of data obtained was done using ANOVA and $\chi 2$ test. Statistically increased titers of Ad-36 virus were seen in obese subjects compared to non-obese controls ($p<0.001$) (Table 1) when viral load was measured using real time PCR SYBR green I fluorescence assay. These observations are in accordance with study conducted by **Atkinson RL et.al (2005)**[6] and **Trovato GM et al. (2009)**[7]

Table 1: Characteristics of the subjects

Variables	**Subjects** (n=20) Mean (s.d.)	**Controls** (n=21) Mean (s.d.)	**p value**
Male/female	11/9	11/10	1.000*
Age(years)	35.6 (1.18)	34.04 (1.32)	0.194+
Weight (kg)	86.7 (10.18)	59.52 (7.41)	<0.001+
Height (m)	1.66 (0.101)	1.64 (0.107)	0.292+
BMI (Kg/m^2)	30.85 (2.20)	18.95 (1.77)	<0.001+
Ad-36 virus	1438.85 (79.24)	615.46 (55.04)	<0.001+

*chi square test x^2 as statistical analysis method
+ ANNOVA as statistical method

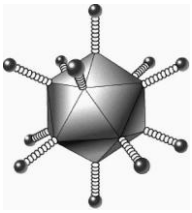


IV. DISCUSSION

Ad-36 was first isolated in 1978 in a diabetic child in Germany.[6]The name is derived from the adenoids, or pharyngeal tonsils, where the first adenovirus was discovered .The adenovirus family is a large family of naked, DNA containing viruses, with a symmetrically icosahedral shape and a diameter ranging from 65–80 nm.[3]They replicate in the nucleus of the infected cell the genome is commonly consists of 36 kb pairs of linear double stranded DNA.[3, 8]Fifty human adenovirus serotypes have so far been described and they have been classified into six sub-groups, A–F. The virus can be transmitted very easily via respiratory, droplet, venereal and fecal–oral routes.[3] In addition to upper respiratory tract infections, they also cause enteritis and conjunctivitis. [3]

The classification of adenovirus 36:

Group: Group I (dsDNA)
Family: Adenoviridae
Genus: Mastadenovirus
Species: Human adenovirus D (HAdV-D)
Serotype: Human adenovirus-36 (HAdV-36)[3]



Many hypotheses have been proposed by **Ginneken VV et al. (2008)** to elucidate the role of Ad-36 virus in causation of obesity.[3]

Hypothesis 1: Increased food intake
It was thought that Ad-36 virus might induce changes in the brain or body, which lead to food cravings.[3] However, animal studies indicated that Ad-36 inoculated animals did not eat more food than the control group. Therefore the hypothesis, that an increase in food intake is unlikely to be the main cause of Ad-36 induced obesity.[3]

Hypothesis 2: Changes in brain morphology
In a study conducted by **Dhurandhar NV et al.** no morphological changes occurred in the brain resulting from Ad-36 infection, suggesting that the mechanism causing obesity is different from that seen in CDV infection.[3] Viral DNA has been isolated in the brains of infected marmosets, although its effects are unknown. Recently it was demonstrated that Ad-36 induces increases in insulin sensitivity, and alters hypothalamic monoamines in rats. We hypothesize, therefore, that obesity in infected individuals may be caused by changes in brain chemistry.[3]

Hypothesis 3: Liver abnormalities
One of the most important organs in lipid metabolism is the liver. It is therefore likely that Ad-36 has an influence on its functioning and performance. But, no morphological alterations have been reported as a result of Ad-36 infection, nor have any chemical changes been discovered.[3]

Hypothesis 4: Adipose tissue
Ad-36 accelerates differentiation of preadipocytes to adipocytes in 3T3-L1 cells, and this has been confirmed in human preadipocytes, as well. This is the most accepted hypothesis.[1,3, 6, ,8 ,9] Viral mRNA expression, although transient, is a prerequisite for enhancing differentiation of preadipocytes by Ad-36.[8] If Ad-36 is a significant factor in the widespread increase in obesity, it is important to investigate possible vaccines to prevent infection, or treatments to alleviate the effects once infected.

Later, **Salehian B et al. (2010)** proposed another mechanism to explain the role of Ad-36 virus in causation of obesity. This includes changes in gene expression of multiple enzymes like sterol regulatory element binding protein I, fatty acid synthases and transcription factors like CCAAT/enhancer binding protein beta, peroxisome proliferator activated receptor gamma and lipoprotein lipase by the virus, which results in increased lipid transport into cells and fatty acid synthesis within cells. These changes are thought to be caused by the action of Ad-36 open reading frame I early region 4 gene.[10]

Further, **Wang ZQ et al. (2010)** proposed that Ad-36 acts on lipid metabolism by reducing fatty acid oxidation and increasing lipogenesis in the cultured skeletal muscle cells and this process is mediated by promoting Cidec/FSP27 expression.[11]

Association of Ad-36 virus with increased body weight and lower serum lipids has been studied extensively .[6]

Na HN et al. (2010) conducted a study to determine an association between Ad-36 virus with obesity and lipid disorders and reported that Ad-36 antibodies are present in 29% of obese and 14% nonobese children.[12]

In contrast to the previous studies, **Goossens VJ et al. (2009)** reported a very low prevalence of human adenovirus-36 (Ad-36) and no evidence of its association with obesity in Dutch and Belgian individuals.[13]

V. CONCLUSION

Thus, from our study it may be concluded that in Indian population there is increased titers of Ad-36 virus in obese individuals than non-obese people. Though obesity has multiple causes, an overlooked possibility is that, in some instances it could be due to an infection. It is possible that viral infections exacerbate and facilitate the development of obesity, or its complications, by working in conjunction with other adipogenic factors. The insidious onset of human obesity makes it is difficult to retrospectively link obesity or any of its co-morbidities to a particular episode of infection. Thus, a causative role for infectious pathogens in human obesity is difficult to establish. Due to ethical considerations, human beings cannot be experimentally infected with these pathogens.[2] In order to determine the role of viral pathogens in human obesity, that is does the Ad-36 virus cause obesity or there are increased titers of virus due to obesity, further research with larger sample size is required.

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