JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Original Article

Adenovirus 36 and its effect on vitamin D levels in obese and overweight patients

Elcin Kal Cakmakliogullari[1], Nurhayat Ozkan Sevencan[2]

[1] Department of Medical Microbiology, Karabuk University Training and Research Hospital,Karabuk,Turkey
[2] Department of Internal Medicine, Karabuk University Training and Research Hospital, Karabuk, Turkey

Abstract

Introduction: The aim of this study was to investigate the prevalence of Adenovirus-36 (Ad-36) in overweight and obese patients and the effects of this virus on some metabolic parameters.

Methodology: The study included 236 female patients with body mass index (BMI) ≥ 25. The patients were separated into 2 groups as overweight (BMI: 25-29.99) and obese (BMI ≥ 30). To quantitatively determine the antibody (Ab) specific to adenovirus type 36 in the serum samples, the enzyme-immunoassay (EIA) method was used (AdV36-Ab, ELISA Kit, MyBioSource). *Laboratory*parameters were compared between patients who are Ad-36 Ab positive and negative.

Results: Of the total 236 patients, 82 (34.7%) were determined as Ad-36 positive and 154 (65.3%) were negative. Ad-36 Ab positivity was statistically significantly higher in the obese group ($p = 0.018$). The HOMA-IR index, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein were found to be the same in both groups with no statistically significant differences($p > 0.05$). Vitamin D levels were significantly higher in BMI ≥ 30 Ad-36 Ab positive group than negative group ($p < 0.05$).

Conclusion: The frequency ofAd-36 Ab positivity was significantly higher in the obese group than in the overweight group. These results can be considered to shed a different perspective from previous reports in literature as only overweight and obese females were included. To the best of our knowledge, this study is the first to have shown that Ad-36 has the effect of elevating the Vitamin D levels.

Key words: Adenovirus-36; obesity; body mass index; vitamin D.

J Infect Dev Ctries 2019; 13(7):665-670. doi:10.3855/jidc.11285

(Received 29 January 2019 – Accepted 26 June 2019)

Introduction

Obesity is a complex, multifactorial disease which has a negative effect on health. Obesity is known to be a cause of Type 2 diabetes primarily and of cardiovascular diseases, hypertension and hyperlipidemia [1].

The World Health Organisation (WHO) has emphasised that obesity is a public health problem in the nature of a global epidemic, defining it as an increase in the amount of fat at a level that negatively affects human health [2].

The most important reasons thought to cause obesity have been shown to be genetic, environmental and endocrine factors. However, the question has arisen of whether pathogen agents have a role in the etiology of obesity as it shows a rapid spread in the same way as contagious diseases. In recent years, infectious agents have been seen as etiological agents in the progression of obesity and the term "infectobesity" has been accepted [3].

The first proven evidence that viruses could have a role in obesity cases was obtained in 1978. To date, a total of 8 viruses have been revelaed which could be a cause of obesity, comprising 3 human viruses, namely adenovirus type 5 (Ad-5), Ad-36, and Ad-37, and 5 animal viruses, namely canine distemper, Rous-associated virus type 7, SMAM-1, Scrapie agent, and Borna disease virus [4].

The aim of this study was to determine the prevalence of Ad-36 in overweight and obese patients and to investigate the effects of this virus on cholesterol, glucose, HOMA-IR and Vitamin D level**s.**

Methodology

Study Sample

The study included 236 female patients, aged 16-67 years, with body mass index (BMI) ≥ 25 who attendent to the Internal Medicine Outpatient Clinic of Karabuk University Training and Research Hospital with the complaint of excess weight between September 2016

and September 2018. Patients with any other disorder that could be a cause of obesity were excluded from the study.

Laboratory Measurements

Serum samples taken from the patients were stored at -80˚C until assay. To determine the antibody (Ab) specific to human Ad-36 in the serum samples, the enzyme-immunoassay (EIA) method was used (AdV36-Ab, ELISA Kit, MyBioSource, San Diego, USA). For the laboratory parameters, theADVIA 1800 system (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA) was used to evaluate fasting and non-fasting glucose, triglycerides, total cholesterol, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) levels and the ADVIA Centaur® XP(Siemens Healthcare Diagnostics Inc, Tarrytown, NY, USA) automated immunoassay system, to evaluate fasting and non-fasting insulin, and Vitamin D levels, and the data were recorded.

To determine insulin resistance, the Homeostatic Model Assessment (HOMA)-Insulin Resistance (IR) index was calculated using the formula [fasting insulin (U/mL) × fasting glucose (mmol/L)] / 22.5.

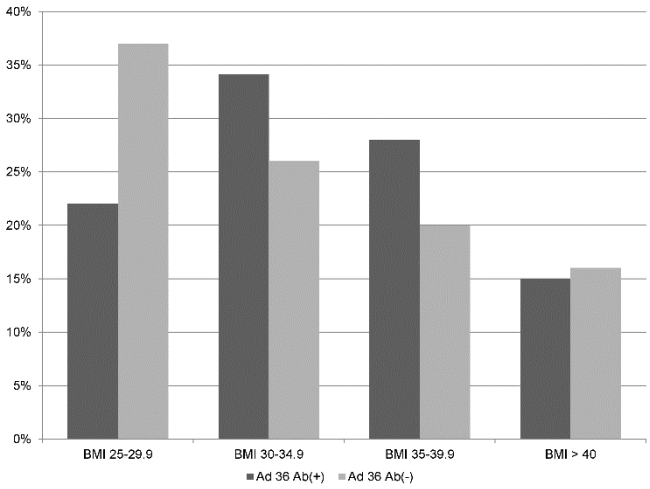
Clinical and Anthropometric Measurements

Body weight was measured withmechanical scales sensitive to 50 grams and height was measured witha wall-mounted scale to 0.1cm values. BMI was calculated (body weight (kg) / height (m^2). The BMI results were evaluatd according to the WHO classification [5].

Statistical Analysis

Data obtained in the study were analysed statistically using IBM SPSS version 24.0 software (IBM Corporation, Armonk, NY, USA). Continuous variables were stated as median (minimum-maximum) values and categorical variables as number (n) and percentage (%). In the analysis of continuous variables between groups, the conformity of data to normal distribution was assessed with the Kolmogorov-Smirnov Goodness of Fit test. Data that did not conform to normal distribution were compared between two groups using the Mann Whitney U-test. The Chi-square test was used in the comparison of categorical variables. A value of $p < 0.05$ was accepted as statistically significant.

Figure 1. Comparison of the presence of adenovirus according to BMI.



Approval for the study was granted by the Local Ethics Committee (No: 77192459-050.99-E.24457)

Results

Ad-36 antibody (Ab) positivity was determined in 82 (34.7%) of the 236 patients included in the study.The patients were separated into 2 groups as Ad-36 Ab positive and negative. The median age of the patients was 40 years (range, 16-67 years) in the Ad-36 Ab positive group and 42 years (range, 17-60 years) in the Ad-36 Ab negative group, with no statistically significant difference determined between the groups ($p > 0.05$) (Table 1). Ad-36 Ab positivity was determined at a statistically significantly higher rate in the obese group compared to the overweight group ($p < 0.05$).(Table 1).

The highest rate of Ad-36 Ab positivity was seen in the BMI range of 30-34.9, but no statistically significant difference was determined between positivity and negativity rates in any of the other BMI range groups ($p > 0.05$) (Figure 1).

Table 1. Sociodemographic data of the groups.

	AdV-36Ab (+) (n = 82)	**AdV-36Ab (-) (n = 154)**	***p***
Age	40 (16-67)	42 (17-60)	0.654*
BMI (kg/m²)			
25-29.99	18 (22.0%)	57 (37.0%)	**0.018****
≥ 30	64 (78.0%)	97 (63.0%)	

* Mann Whitney U Test; ** Chi-square Test (Linear by linear association); AdV-36 Ab: Adenovirus-36 Antibody, BMI: Body mass index.

Table 2. Comparisons of clinical parameters according to the presence of adenovirus.

	AdV-36 Ab (+) (n = 82)	**AdV-36 Ab (-) (n = 154)**	***p***
	Median (Min-Max)		
Fasting glucose (mg/dL)	96 (66-139)	95 (71-171)	0.517
Triglycerides (mg/dL)	121 (41-422)	129 (45-929)	0.121
Total cholesterol (mg/dL)	185.5 (124-318)	194 (110-375)	0.407
HDL (mg/dL)	46.9 (9.5-84.8)	49.8 (31.2-91.3)	0.461
LDL (mg/dL)	113 (12-238)	111.5 (50-253.4)	0.951
Non-fasting glucose (mg/dL)	102 (67-209)	106 (45-244)	0.934
Fasting insulin (µU/mL)	13 (5.2-61.9)	13.1 (2.7-300)	0.827
Non-fasting insulin (µU/mL)	49 (6.4-300)	54 (10.1-82)	0.368
Vitamin D (ng/mL)	9.5 (4.2-78.3)	8.4 (4.2-63.2)	0.145
HOMA-IR index	3.1 (1.1-13.4)	3.1 (0.5-19.7)	0.948

Mann Whitney U Test; AdV-36 Ab: Adenovirus-36 Antibody; HDL: High-density lipoprotein, LDL: Low density lipoprotein; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance.

Table 3. Comparison of the laboratory parameters of the Ad-36 Ab positive and negative groups according to BMI values.

	Ad-36 (+) (n = 82) Median (Min-Max)			**Ad-36 (-) (n = 154) Median (Min-Max)**		
	BMI (25-29,99) (n = 18)	**BMI (≥ 30) (n = 64)**	***p***	**BMI (25-29.99) (n = 57)**	**BMI (≥ 30) (n = 97)**	***p***
Fasting glucose (mg/dL)	90 (78-109)	98 (66-139)	**0.005***	90 (71-116)	98 (76-171)	**< 0.001***
Triglycerides (mg/dL)	84.5 (42-358)	131 (41-422)	**0.001***	104 (45-929)	141 (52-401)	**0.001***
Total cholesterol (mg/dL)	175 (124-229)	186 (135-318)	0.096*	181 (118-252)	199 (110-375)	0.096*
HDL (mg/dL)	52.7(9.5-77.9)	45.6 (30.7-84.8)	**0.027***	51.7 (31.6-91.3)	47.2 (31.2-75.8)	0.064*
LDL (mg/dL)	96.5 (12-161)	115 (55-238)	**0.013***	106 (52-171)	119 (50-253.4)	0.132*
Non-fasting glucose (mg/dL)	97 (67-130)	105 (77-209)	**0.007***	97 (64-196)	108.5 (45-244)	**0.004***
Fasting insülin (µU/mL)	9.6 (6.7-16.2)	14.7 (5.2-61.9)	**< 0.001***	10.5 (2.7-79.9)	14.8 (3.5-82)	**< 0.001***
Non-fasting insulin (µU/Ll)	40.7 (6.4-101)	54.1 (10.6-300)	**0.049***	44.1 (10.4-206.5)	61.4 (10.1-300)	**0.030***
Vitamin D (ng/mL)	7.7 (4.2-29.6)	9.9 (4.2-78.3)	**0.024***	9 (4.2-58.9)	8.1 (4.2-63.2)	0.554*
HOMA-IR index	2.1 (1.6-3.5)	3.5 (1.1-13.4)	**< 0.001***	2.3 (0.5-19.7)	3.5 (0.8-18.6)	**< 0.001***

* Mann Whitney U Test; AdV-36 Ab: Adenovirus-36 Antibody, HDL: High-density lipoprotein, LDL: Low density lipoprotein; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance.

Table 4. Comparison of the laboratory parameters of the Ad-36 Ab positive and negative groups with BMI ≥ 30 and BMI 25-29.99.

	BMI (≥ 30) (n = 161)			**BMI (25-29.99)**		
	Ad-36 Ab (+) (n = 64)	**Ad-36 Ab (-) (n = 97)**	***p***	**Ad 36-Ab (+) (n = 18)**	**Ad-36 Ab (-) (n = 57)**	***p***
Fasting glucose (mg/dL)	98 (66-139)	98 (76-171)	0.935*	90 (78-109)	90 (71-116)	0.847*
Triglycerides (mg/dL)	131 (41-422)	141 (52-401)	0.111*	84.5 (42-358)	104 (45-929)	0.066*
Total cholesterol (mg/dL)	186 (135-318)	199 (110-375)	0.347*	175 (124-229)	181 (118-252)	0.203*
HDL (mg/dL)	45.6 (30.7-84.8)	47.2 (31.2-75.8)	0.629*	52.7 (9.5-77.9)	51.7 (31.6-91.3)	0.537*
LDL (mg/dL)	115 (55-238)	119 (50-253.4)	0.856*	96.5 (12-161)	106 (52-171)	0.199*
Non-fasting glucose (mg/dL)	105 (77-209)	108.5 (45-244)	0.887*	97 (67-130)	97 (64-196)	0.341*
Fasting insülin (µU/mL)	14.7 (5.2-61.9)	14.8 (3.5-82)	0.575*	9.6 (6.7-16.2)	10.5 (2.7-79.9)	0.385*
Non-fasting insulin (µU/mL)	54.1 (10.6-300)	61.4 (10.1-300)	0.354*	40.7 (6.4-101.7)	44.1 (10.4-206.5)	0.280*
Vitamin D (ng/mL)	9.9 (4.2-78.3)	8.1 (4.2-63.2)	**0.036***	7.7 (4.2-29.6)	9 (4.2-58.9)	0.441*
HOMA-IR index	3.5 (1.1-13.4)	3.5 (0.8-18.6)	0.593*	2.1 (1.6-3.5)	2.3 (0.5-19.7)	0.399*

* Mann Whitney U Test; AdV-36 Ab: Adenovirus-36 Antibody, HDL: High-density lipoprotein, LDL: Low density lipoprotein; HOMA-IR: Homeostatic Model Assessment-Insulin Resistance.

The two groups were compared in respect of fasting and non-fasting glucose, triglycerides, total cholesterol, HDL, LDL, fasting and non-fasting insulin, vitamin D and HOMAR-IR levels. No statistically significant difference was determined between the groups ($p > 0.05$) (Table 2).

The laboratory parameters were compared between the Ad-36 Ab positive and negative groups with BMI of 25-29.99 and BMI ≥ 30. In the adenovirus positive group, a statistically significant difference was determined between those with BMI ≥ 30 and those with BMI 25-29.99 in respect of fasting and non-fasting glucose, triglycerides, HDL, LDL, fasting and non-fasting insulin, vitamin D and HOMA-IR levels ($p < 0.05$). In the adenovirus negative group, a statistically significant difference was determined between those with BMI ≥ 30 and those with BMI 25-29.99 in respect of fasting and non-fasting glucose, triglycerides, fasting and non-fasting insulin, and HOMA-IR levels ($p < 0.05$) (Table 3).

When the laboratory parameters were compared between the Ad-36 Ab positive and negative groups with BMI of 25-29.99 and BMI ≥ 30, vitamin D was found to be statistically significantly high in the groups with BMI ≥ 30 ($p < 0.05$) (Table 4).

Discussion

Obesity, which is a risk factor for several chronic diseases, causing a serious increase in morbidity and mortality, is a factor that can be changed. Together with an increasing prevalence of obesity, there has been an increase in the incidence of diseases related to obesity [6]. In recent years there has been a global increase in obesity with a rapid spread similar to that of contagious diseases, suggesting that there could be a relationship with infectious causes, especially with viruses [7].

In several experimental animal studies, despite an increase, Ad-36 deoxyribonucleic acid (DNA) determination was also reported in the adipose tissue of the animals infected with Ad-36. However, no isolation of Ad-36 DNA in skeletal muscles, brain or the thalamus of these animals, has indicated that the adipose tissue is the target tissue.As it is not possible from an ethical perspective to innoculate humans, Ad-36 has not been proven as a cause of human obesity [8-11].

Clinical studies conducted on paediatric and adult age groups have shown that there could be a relationship between Ad-36 and obesity [12-15]. In a meta-analysis by Shang et al, which included 5739 subjects, a relationship between Ad-36 and obesity was clearly confirmed [16]. Atkinson et al screened 89 pairs of twins for Ad-36, Ad-2, Ad-31 and Ad-37 antibody positivity, and significantly high BMI and high body fat percentage were determined in twins with Ad-36 Ab positivity. When it is considered that the twins had similar demographic characteristics and were exposed to the same environmental factors, the findings of that study provided great support for the hypothesis that Ad-36 increased adiposity in humans [17].

Obesity associated with Ad-36 is thought to be initiated with the effect of the open reading frame 1 of the early region 4 gene (E4 ORF1) of the virus, and it then progresses with adipocyte proliferation and differentiation [18,19]. In a study conducted to provide evidence of this, it was shown that when pre-adipocytes were innoculated invitro by transferring E4 ORF1 gene of Ad-36 to retroviruses, fat accumulation increased [18]. In the current study, Ad-36 Ab positivity was determined to be statistically significantly higher in the obese group than in the overweight group. According to the current study data, it was thought that the rapidly progressing weight gain associated with Ad-36 caused BMI of > 30.

Weight gain is known to increase the risk of diabetes, and obesity is seen in the etiology of 65% of Type 2 diabetes mellitus (T2DM) patients [20]. Previous invitro studies have shown that in those infected with Ad-36, Glucose transporter1 (GLUT1) and GLUT4 mediated glucose uptake in preadipocytes, adipocytes and myoblasts is increased with the activation of E4 ORF1 protein Ras and phosphoinositide 3 kinase, and glucose regulation is achieved with non-insulin mechanisms by reducing glucose output in the liver cells [21-23]. In another study of 1507 subjects, those infected with Ad-36 were seen to achieve better glycaemic control [24]. Therefore, it has been thought that in the future, Ad-36 could be used in the treatment of T2DM [25].

In the current study, there was no statistically significant difference between the Ad-36 Ab positive and negative groups in respect of fasting and non-fasting glucose, fasting and non-fasting insulin and the HOMA-IR index. Moreover, the fasting glucose (96; 95 mg/dL) and fasting insulin (13; 13.1 μU/mL) median values were very close and the HOMA-IR index (3.1; 3.1) median values in the two groups were exactly the same. The non-fasting glucose and non-fasting insulin median values were found to be lower in the Ad-36 Ab positive patients compared to the negative group (glucose 102;106 mg/dL, insulin 49;54 μU/mL). These findings suggest that the non-insulin mechanisms of Ad-36 had come into action in glucose regulation.

In cases of obesity associated with adenoviruses, the lipid profiles show variations. In rat and chicken model studies, Dhuranhard et al reported that the serum triglyceride and cholesterol levels of the group infected with Ad-36 were lower than those of the control group [26]. In a study of 502 volunteers and 89 pairs of twins, Atkinson et al found serum cholesterol and triglyceride levels to be lower in Ad-36 positive subjects compared to the negative group, but in examination of the twins, there was no significant difference between the Ad-36 Ab positive and negative groups [17]. It was reported in a meta-analysis of 10 observational studies that there was no correlation between Ad-36 positivity and HDL, triglyceride and total cholesterol levels, and there was only a significant increase in the LDL level [9]. In the current study, while no statistically significant difference was found between the two groups, the total cholesterol 185.5;194 mg/dL), triglyceride (121;129mg/dL) and HDL (46.9; 49.8 mg/dL) values were found to be lower and the LDL (113;111.5 mg/dL) level was higher in the Ad-36 Ab positive group than in the negative group. In the comparisons of the Ad-36 positive and negative groups according to the BMI values, it was determined that as BMI increased there was a significant increase in fasting and non-fasting glucose, triglycerides, fasting and non-fasting insulin and HOMA-IR values. Moreover, while the decrease in HDL and increase in LDL and vitamin D were found to be significant in the Ad-36 positive group, this was not the case in the Ad-36 negative group. These data suggest that the increase in BMI could be independent of the effect of Ad-36 positivity.

Previous studies have shown a decrease in Vitamin D in parallel with increasing BMI levels [27-29]. In the current study, Ad-36 Ab positivity was statistically significantly higher in the obese group than in the overweight group.Although there was no statistically significant difference between the Ad-36 Ab positive and negative groups in respect of Vitamin D, the median values were found to be higher in the Ad-36 positive group (9.5;8.4 ng/mL).When the vitamin D values of the Ad-36 positive and negative groups were compared according to the BMI values, when BMI increased in the Ad-36 Ab negative group, vitamin D decreased, but no significant difference was found. In contrast, when BMI increased in the Ad-36 positive group, there was determined to be a significant increase in vitamin D. Furthermore, when the Ad-36 Ab positive and negative groups with BMI ≥ 30 were compared, a statistically significant increase was determined in the positive group.

To the best of our knowledge, there has been no previous study in literature that has evaluated Vitamin D in Ad-36-related obesity. The current study data are not consistent with previous findings that Vitamin D decreases as BMI increases in obesity which has developed for multifactorial reasons. This suggests that the positive contribution of Ad-36 to glucose regulation could also be found in Vitamin D. Further studies are needed to provide evidence for this hypothesis.

All the participants in the current study were females with BMI ≥ 25. With the inclusion of only female patients, sex hormone-related effects were eliminated. Thus, it was aimed to assess the effect of Ad-36 Ab alone as an independent variable in obesity, which is a multifactorial health problem of unknown cause. Further studies are required to obtain clearer data which would reflect the effects of Ad-36 in obesity that was thought to be associated with Ad-36.

Conclusion

In conclusion, the results of this study demonstrated that Ad-36 Ab was statistically significantly higher in the obese group (BMI ≥ 30) than in the overweight group. This study can be considered to provide a different perspective from previous studies in literature as only overweight and obese females were included in the sample and the only independent variable was Ad-36 Ab. As all the patients were overweight or obese they all had the same risk factors, and although no statistically significant difference was found in the laboratory parameters, the numerical differences in the values were consistent with previous reports in literature. To the best of our knowledge, there has been no previous study in literature that has evaluated Vitamin D in Ad-36-related obesity. Therefore, this is the first study to show that Ad-36 has the effect of increasing the level of Vitamin D. Nevertheless, there is a need for further large-scale studies to confirm these findings.

References

1. Mokdad AH, Ford ES, Bowman BA, Dietz WH, Vinicor F, Bales VS, Marks JS (2003) Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. Jama, 289*:* 76-79.
2. World Health Organization (2000) Obesity: Preventing and managing the global epidemic report of a WHO consultation on obesity. Geneva, World Health Organ Tech Rep Ser 894: 1-253.
3. Dhurandhar NV (2001) Infectobesity: obesity of infectious origin. J.Nutr 131: 2794-2797.
4. Tuncer P, Yesilbag K (2008) Viral etiology in obesity Turk J Infec 22: 241-249 [Article in Turkish]
5. World Health Organization (2016)Obesity and Overweight Fact Sheet No: 311, Geneva, WHO. Available:

http//www.who.int/mediacentre/factsheets/fs311/enAccessed: 10 March 2019
6. Bray GA (2004) Medical consequences of obesity. J ClinEndocrinolMetab 89: 2583-2589.
7. Atkinson RL (2007) Viruses as an etiology of obesity. Mayo Clin Proc 82: 1192-1198.
8. Dhurandhar NV, Israel BA, Kolesar JM, Mayhew G, Cook ME, Atkinson RL (2001) Transmissibility of adenovirus-induced adiposity in a chicken model. Int J Obes25: 990-996.
9. Dhurandhar NV, Israel BA, Kolesar JM, Mayhew GF, Cook ME, Atkinson RL (2000) Increased adiposity in animals due to a human virus. Int J Obes 24: 989-996.
10. Dhurandhar NV, Whigham LD, Abbott DH (2002) Human adenovirus Ad-36 promotes weight gain in male rhesus and marmoset monkeys. J Nutr 132: 3155-3160.
11. Whigham LD, Israel BA, Atkinson RL (2006) Adipogenic potential of multiple human adenoviruses in vivo and *in vitro* in animals. Am J Physiol Regul Integr Comp Physiol 290: 190-196.
12. Almgren M, Atkinson R, He J, Hilding A, Hagman E, Wolk A,Thorell A, Marcus C,Näslund E, Östenson CG,Schalling M,Lavebratt C(2012) Adenovirus-36 is associated with obesity in children and adults in Sweden as determined by rapid ELISA. PLoS One 7: e41652.
13. Parra-Rojas I, Del Moral-Hernandez O, Salgado-Bernabe AB, Guzman-Guzman IP, Salgado-Goytia L, Munoz-Valle JF (2013) Adenovirus-36 seropositivity and its relation with obesity and metabolic profile in children. Int J Endocrinol 2013: 463194.
14. Ponterio E, Cangemi R, Mariani S, Casella G, De Cesare A, Trovato F,Garozzo A, Gnessi L (2015) Adenovirus 36 DNA in human adipose tissue. Int J Obes 39: 1761-1764.
15. Cakmakliogullari EK, Sanlidag T, Ersoy B, Akcali S, Var A, Cicek C (2014) Are human adenovirus-5 and 36 associated with obesity in children? J Investig Med62: 821-824.
16. Shang Q, Wang H, Song Y, Weı L, Lavebratt C, Zhang F, Gu H (2014) Serological data analyses show that adenovirus 36 infection is associated with obesity: a meta-analysis involving 5739 subjects. Obesity 22: 895-900.
17. Atkinson RL, Dhurandhar NV, Allison DB (2005) Human Ad-36 is associated with increased body weight and paradoxical reduction of serum lipids. Int J Obes 29: 281-286.
18. Rogers PM, Fusinski KA, Rathod MA, Loiler SA, Pasarica M, Shaw MK, Gimble JM (2008) Human adenovirus Ad-36 induces adipogenesis via its E4 orf-1 gene.Int J Obes32: 397-406.
19. Vangipuram SD, Sheele J, Atkinson RL, Holland TC, Dhurandhar NV (2004) A human adenovirus enhances preadipocyte differentiation.,Obes Res 12: 770-777.
20. George AB (2004) Medical Consequences of obesity.J Clin Endocrinol Metab 89: 2583–2589.
21. Wang ZQ, Cefalu WT, Zhang XH, Yu Y, Qın J, Son L, Rogers PM, Mashtalır N, Bordelon JR, Ye J, Dhurandhar NV (2008) Human adenovirus type 36 enhances glucose uptake in diabetic and nondiabetic human skeletal muscle cells independent of insulin signalling. Diabetes57: 1805-1813.
22. Dhurandhar EJ, Dubuısson O, Mashtalır N, Krıshnapuram R, Hedge V, Dhurandhar NV (2011) E4orf1: novel ligand that improves glucose disposal in cell culture. PLoS One6: e23394.
23. Na HN, Dubuısson O, Hedge V, Nam JH, Dhurandhar NV (2016) Human adenovirus AD36 and its E4orf1 gene enhance cellular glucose uptake even in the presence of inflammatory cytokines. Biochimie124: 3-10.
24. Krishnapuram R, Dhurandhar EJ, Dubuisson O, Kirk-Ballard H, Bajpeyi S, Butte NF, Gupta AK (2011) A template to improve glycemic control without reducing adiposity or dietary fat. Am J PhysiolEndocrinolMetab300: 779-789.
25. Kumar M, Kong K, Javıer RT (2014) Hijacking Dlg1 for oncogenic phosphatidylinositol 3-kinase activation in human epithelial cells is conserved mechanism of human adenovirus E4-ORF1 proteins. J Virol 88: 14268-14277.
26. Dhurandhar NV, Israel BA, Kolesar JM, Mayhew GF, Cook ME, Atkinson RL (2000) Increased adiposity in animals due to a human virus. Int. J. Obes. Relat. Metab. Disord24: 989-996.
27. Need AG, O'Loughlin PD, Horowitz M, Nordin BE (2005) Relationship between fasting serum glucose, age, body mass index and serum 25 hydroxyvitamin D in postmenopausal women. Clin Endocrinol 62:738-741.
28. Konradsen S, Ag H, Lindberg F, Hexeberg S, Jorde R (2008) Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index. Eur J Nutr 47: 87-91.
29. Muscogiuri G, Sorice GP, Prioletta A, Policola C, Della Casa S, Pontecorvi A, Giaccari A (2010) 25-Hydroxyvitamin D concentration correlates with insulin-sensitivity and BMI in obesity. Obesity18: 1906-1910.

Corresponding author
Elcin Kal Cakmakliogullari
Department of Medical Microbiology, Karabuk University Training and Research Hospital
Karabuk,Turkey
Tel: 370-4158000
Fax: 370-4125628
Email: drelcinkal@yahoo.com

Conflict of interests: No conflict of interests is declared.