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The relationship between adenovirus-36 seropositivity, obesity and metabolic profile in Turkish children and adults

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SUMMARY

Obesity potentially arising from viral infection is known as 'infectobesity'. The latest reports suggest that adenovirus-36 (Adv36) is related to obesity in adults and children. Our aim was not only to determine the Adv36 seropositivity in both obese and non-obese children and adults, but also to investigate correlations between antibody positivity and serum lipid profiles. Both Adv36 positivity and tumour-necrosis-factor-alpha, leptin and interleukin-6 levels were detected in blood samples collected from 146 children and 130 adults by ELISA. Fasting plasma triglycerides, total cholesterol and low-density lipoprotein levels were also measured. Adv36 positivity was determined to be 27·1% and 6% in obese and non-obese children and 17·5% and 4% in obese and non-obese adults, respectively. There was no difference with regard to total cholesterol, low-density lipoprotein, triglyceride, tumour-necrosis-factor-alpha and interleukin-6 levels ($P > 0{\cdot}05$). However, there was a significant difference between groups in terms of leptin levels ($P < 0{\cdot}05$). We determined the prevalence of Adv36 positivity in obese children and adults. Our results showed that Adv36 may be an obesity agent for both adults and children, parallel with current literature data. However, the available data on a possible relationship between Adv36 infection and obesity both in children and adults do not completely solve the problem.

Key words: Adenovirus-36, children, infectobesity, leptin.

INTRODUCTION

Obesity has become one of the most prevalent chronic disorder that affects large populations throughout the world [1]. The possible mechanism associated with the development of obesity is not largely understood, although it seems to be associated with a great number of factors, including endocrine, neural, genetic and behavioural as well as environmental conditions in the context of both children and adults [2]. As obesity appears to have a key role in many health conditions, including hypertension, coronary heart disease, stroke and some types of cancer, preventing obesity is an important public health issue throughout the world. The causal factors related with obesity should therefore be identified to prevent these obesity-related diseases. Additionally, some serum lipid parameters such as tumour necrosis factor-alpha (TNF-α), interleukin-6 (IL-6) and leptin have important roles in the aetiology of obesity. Leptin, a hormone that plays a key role in

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regulating energy intake and energy expenditure, may be one of the most important factors with regards to this disease [3].

On the other hand, despite its multifactorial aetiology, traditional obesity treatment or prevention strategies offer a comprehensive approach, mostly irrespective of obesity's cause. If the contribution of different factors to obesity is identified, effective cause-specific treatment strategies may be developed. If certain infections contribute to obesity, prevention or treatment approaches for such a subgroup of obesity could differ from common and long-term lifestyle changes. Nonetheless, identifying adipogenic microbes and determining their causative role in human adiposity is challenging [4].

Infectobesity has largely been overlooked. Increased adiposity has been investigated in animal models following infection with animal viruses, canine distemper virus [5–7], Rous-associated virus [8, 9], an avian adenovirus, SMAM-1 [10] and the human adenovirus-36 (Adv36) [11–13]. Adv36 was first isolated in 1980 and belongs to the group of 56 known human adenovirus serotypes and seven subgroups based on their immunochemical responses, nucleic acid characteristics, hexon and fibre protein characteristics, biological properties and phylogenetic analysis. Adv36 is a non-enveloped icosahedral virus comprising double-stranded DNA [14] and generally causes infections such as cold-like symptoms, gastroenteritis, and conjunctivitis [15]. The latest reports from researchers in North America, Denmark, Korea and Italy suggest that Adv36 is related to obesity in adults and children [16–21]. It has been shown that experimental and natural Adv36 infection of multiple animal species resulted in obesity through increasing proliferation and differentiation of pre-adipocytes, lipid accumulation in mature adipocytes and reducing cells' leptin secretion and expression, but also increasing differentiation of pre-adipocytes [10, 12, 22–27].

In the beginning of the experiments, Adv36 was capable of inducing adiposity in experimentally infected mice, chickens and non-human primates [28]. Like other animals, the presence of Adv36 antibodies in humans is associated with increased body mass index (BMI) [26]. Most previous studies regarding this issue used the serum neutralization assay to detect antibodies against Adv36, but the assay is quite expensive and time consuming, usually taking about 1–2 weeks to perform. It is therefore not appropriate for rapid screening in the case of Adv36 infection [29]. In this study, we tested that Adv36 was present within the Turkish population and that it was associated with obesity in children and adults in the Eastern area of Turkey; moreover, we found it was associated with lower leptin levels by using the enzyme-linked immunosorbent assay (ELISA).

MATERIALS AND METHODS

Ethics statement and participants

A total of 276 participants (146 children, 130 adults) from Erzurum, Turkey were studied in this project. This project was approved by the Non-Drug Clinical Trials Ethical Committee of Ataturk University, Medical Faculty (no. 2 036 991/68·00-349). The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

We studied obese children aged 5–17 years (mean 10·6 ± 3·7 years) who had been referred to the paediatric endocrinology clinic at Ataturk University Medical Faculty Research and Application Hospital in Erzurum, Turkey. Blood samples and clinical data from 96 obese children, including 55 girls and 41 boys, were collected. The children were sampled before any treatment for obesity. Additionally, 50 lean controls, including 33 girls and 17 boys, aged 5–16 years (mean 10·5 ± 3·7 years) were included from the Paediatric Endocrinology Clinic at Ataturk University, Research and Application Hospital.

Obese adults aged 25–48 years (mean 40·4 ± 8·3 years) referred to the Internal Medicine (Endocrinology) Clinic and Acupuncture and Alternative Therapies Research & Application Centre were also studied. Blood samples and clinical data from 80 obese adults, including 57 women and 23 men, were collected. Additionally, 50 lean controls, including 23 women and 27 men, aged 23–49 years (mean 37·8 ± 8·4 years) were included from the Internal Medicine (Endocrinology) Clinic at Ataturk University, Research and Application Hospital.

Clinical data collection

In the study, body weight of participants, wearing lightweight clothes and without shoes, was determined and height was measured to the nearest 1 mm using a stadiometer. From these measurements, the researchers calculated BMI (weight/height^2, kg/m^2).

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The classification of normal weight and obesity was made using the 2000 Center for Disease Control and Prevention growth charts defining normal weight as 5th to 85th percentiles, and obesity as ⩾95th percentile. Clinical data available for all patients included levels for fasting plasma triglycerides (TG), total cholesterol (TC) and low-density lipoprotein (LDL). These levels were measured by the Ataturk University Hospital's accredited biochemistry laboratory. After blood coagulation, serum was separated by centrifugation, collected and kept frozen at -80 °C until analysis.

Other measurements and ELISA for antibodies against Adv36

TNF-α, IL-6 (DIAsource ImmunoAssays, Belgium) and leptin (Enzo, Belgium) levels were measured using a commercially available ELISA. A qualitative determination using ELISA on the antibodies to define Adv36 in the serum samples (Adv36-Ab kit, Cusabio, China). All chemicals and 96-well ELISA microplates were brought to room temperature before the study. The first well was blank, the second and third wells were for positive and negative controls, respectively. A serum dilution (1:10) was added to each well. After incubation (at 37 °C, for 30 min) and washing, a 100 μl mixture of horseradish peroxidase (HRP-conjugated coating protein) was added to each well other than the first well. After further washing, respectively 50 μl of solution A and solution B were added and incubated at 37 °C for 10 min under darkened conditions. Finally, a 50 μl stop solution was added to the wells and the plate was read at a wavelength of 450 nm.

Statistical analysis

All values are quoted as median (interquartile range) and statistical analysis performed using SPSS v. 20.0 (SPSS Inc., USA). One-way ANOVA, Mann–Whitney *U* and Student's *t* tests were used for statistical analyses.

RESULTS

A total of 146 children (58 boys, 88 girls) were enrolled in the study. Of those children, 96 were obese and 50 were non-obese. In the same way, 130 adults (50 men, 80 women) were enrolled in the study. Of those, 80 were obese and 50 were non-obese. There were no significant differences in age, sex and BMI in the obese and non-obese groups ($P > 0{\cdot}05$). Overweight and obese individuals were significantly heavier than normal weight individuals. Adv36 seropositivity tended to have a higher prevalence in obese children than in the normal-weight group (27·1% *vs.* 6%, $P < 0{\cdot}05$). Adv36 was present in 26 obese children and three non-obese children. Additionally, Adv36 seropositivity also had a higher prevalence in obese adults than in the normal-weight group (17·5% *vs.* 4%, $P < 0{\cdot}05$). Adv36 was present in 14 obese adults and two non-obese adults. The proportion of Adv36 positivity of obese and non-obese children, and that in adults, is shown in Figure 1.

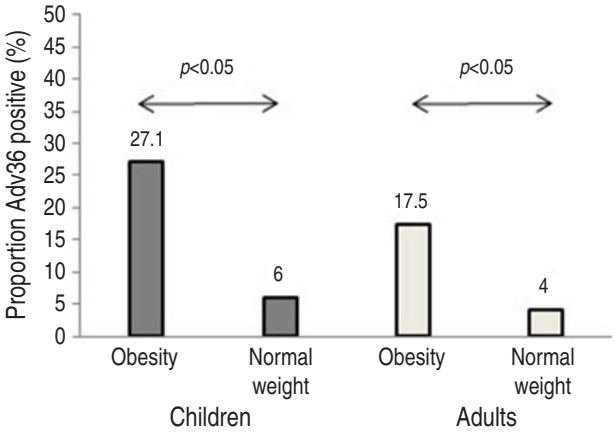

Fig. 1. The proportion of adenovirus-36 (Adv36) positivity in obese and non-obese children and adults.

Gender and age did not significantly differ according to Adv36 status. In addition, no differences in LDL, TG and TC according to Adv36 antibody status were found in the normal-weight group for both the children and adult groups. All clinical and biochemical characteristics according to Adv36 seropositivity are shown in Table 1.

According to the data we obtained, no significant differences in TNF-α and IL-6 levels between Adv36-positive and Adv36-negative groups for both children and adults were found. However, there were significant differences between both obese children and adults in terms of leptin levels ($P < 0{\cdot}05$). Interestingly, leptin levels were lower in Adv36-positive children and adults than Adv36-negative children and adults (Fig. 2).

DISCUSSION

Adenoviruses are DNA viruses that are most generally related to upper respiratory tract infections or

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Table 1. *Clinical and biochemical characteristics according to adenovirus-36 (Adv36) seropositivity*

	Obese children ($n = 96$)				Obese adults ($n = 80$)			
	Adv36(+) ($n = 26$)		Adv36(–) ($n = 70$)		Adv36(+) ($n = 14$)		Adv36(–) ($n = 66$)	
	Value	S.D.	Value	S.D.	Value	S.D.	Value	S.D.
Height (cm)	147·1	18·8	143·1	21·0	158·2	6·6	158·0	6·5
Weight (kg)	65·6	17·8	59·6	17·6	85·4	10·2	93·0	13·7
BMI (kg/m^2)	32·7	2·4	33·2	2·3	34·9	2·8	37·4	5·9
TNF-α (pg/ml)	35·9	11·5	34·1	10·2	30·0	8·0	29·7	9·2
IL-6 (pg/ml)	33·5	14·9	22·2	13·5	80·7	65·3	44·8	24·6
Leptin (pg/ml)	138·6	32·4	275·6	131·5	148·8	50·1	255·6	161·1
LDL (mg/dl)	133·5	26·9	130·1	38·2	131·9	29·4	152·3	38·7
TG (mg/dl)	172·1	90·9	161·7	74·3	104·5	43·9	136·5	69·2
TC (mg/dl)	189·6	33·9	174·9	32·0	180·1	36·3	197·9	45·3

BMI, Body mass index; TNF-α, tumour necrosis factor-α; IL-6, interleukin-6; LDL, low-density lipoprotein; TG, triglycerides; TC, total cholesterol.
The parametric variables shown are mean ± S.D.; median, and 5th and 95th percentiles are shown for non-parametric variables.

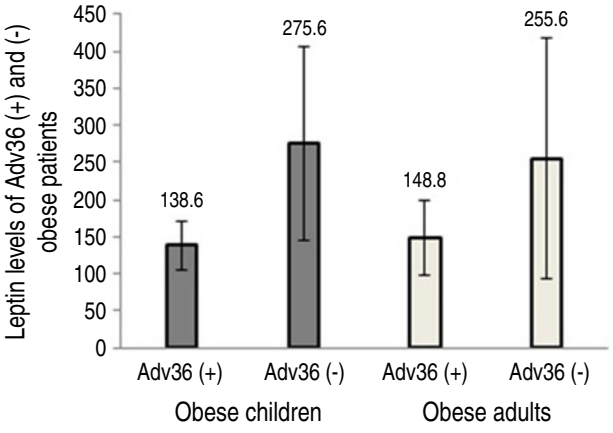

Fig. 2. Leptin levels of adenovirus-36 (Adv36) positivity and negativity in obese children and adults.

enteritis. Although the exact mechanism through which Adv36 might contribute to human obesity remains unknown, studies have shown that infection of non-human primates, rodents and chickens with Adv36 increased total body fat independent of energy intake [12]. Several mechanisms have been tried to explain the association between Adv36 infection and obesity. For instance, in the rodent model, Adv36 decreases hypothalamic monoamine levels and is associated with the decreasing amount of corticosterone secretion [24], which leads to impaired fatty-acid metabolism. Moreover, alterations in both leptin expression and glucose metabolism have been described and may contribute to increased fat accumulation in animals exposed to Adv36 infection [27].

The primary aim of this study was to assess the relationship between the presence of Adv36 antibodies and obesity both in children and adults. Indeed, we also found that the percentage of Adv36 antibody-positive participants was significantly higher in the obese groups compared to the non-obese groups. The data supports an association between the presence of Adv36 positivitiy and obesity both in children and adults. Our findings are fairly consistent with results reported earlier. Additionally, in a study performed in adults from three US cities it was reported that 30% of obese individuals were Adv36 antibody-positive compared to only 11% of non-obese adults. Although the prevalence of Adv36 positivity in obese individuals differed considerably in the three cities, the city analysis showed that it was significantly higher in obese participants than in corresponding non-obese participants [16].

Several studies determining the prevalence of Adv36 antibodies in obese people have been performed in the United States as well as Italy, Korea and The Netherlands. One of these is the study performed in 2009 by Trovato *et al.* [30] showing that the prevalence of Adv36 was 65% and 33% in obese and non-obese participants (203 participants, mean age 45·9 years), respectively. It is interesting that percentages of Adv36 positivity both in obese and non-obese participants were quite similar in the US study and our study in Turkey, although the two studies were performed under different conditions. In our study there were 80 obese and 50 non-obese adults

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aged 23–49 years. Adv36 seropositivity also had a higher prevalence in obese adults than in the normal-weight group (17·5% *vs.* 4%, $P < 0·05$).

On the other hand, several studies have also been performed to determine the prevalence of Adv36 positivity in children from different countries. Two publications from Korea provided initial data on the prevalence of Adv36 antibodies in children. One of these reported the presence of Adv36-specific antibodies in 30% of children attending an obesity clinic in Seoul, South Korea [17]. In another study of the Ewha Woman's University Medical School Obesity Research Study, 255 obese and 59 non-obese Korean schoolchildren aged between 6 and 15 years were evaluated for Adv36 antibody positivity. In that population, Adv36 antibodies were twice as prevalent in the obese children as in the non-obese children [19].

A cross-sectional study of 124 children reported that Adv36 positivity was detected in 19 (15%) children. Moreover, Adv36 positivity was significantly more frequent in obese children (22%) than non-obese children (7%) [31]. Another study performed in 157 children (75 normal weight, 82 obese) on this issue showed that a significant association between Adv36 seropositivity and obesity was present in the children. Adv36 seropositivity had a higher prevalence in obese children than in the normal-weight group (58·6% *vs.* 41·4%, $P = 0·007$) [32]. However, in a study of 509 participants from The Netherlands and Belgium, no significant association between Adv36 seropositivity and obesity was found. The overall Adv36 seroprevalence was 5·5% (3·9% in non-obese, 5·7% in obese subjects) [33].

To compare, in our study there were 96 obese and 50 non-obese children aged 5–17 years. Adv36 seropositivity had a higher prevalence in obese children than in the normal-weight group (27·1% *vs.* 6%, $P < 0·05$). There is only one other study that has been performed for detection of Adv36 seropositivity both in children and adults. In this, Almgren *et al*. examined the presence of antibodies against Adv36 in serum by using ELISA in 1946 individuals including 424 children and 1522 adults. Their study reported that Adv36 positivity was associated with paediatric obesity and with severe obesity in adult females compared to lean and obese patients, with a 1·5- to 2-fold Adv36 positivity increase in cases [29]. These findings are quite similar to our study. We had a total 276 participants (146 children, 130 adults) and Adv36 positivity was in fact associated with paediatric obesity, and with obesity in adults according to the data.

Besides these studies, the mechanisms of alterations in serum lipids and other cytokines in both obese and non-obese individuals are unknown. Some serum lipid parameters may show differences in some studies. Acute viral infections may lower serum cholesterol, but often produce elevations in serum TGs [7]. It has been shown in Swedish patients that Adv36 infection is associated with paediatric obesity, severe obesity in adult females and lower risk of high blood lipid levels [29]. Moreover, Adv36 seropositivity was assessed in 68 obese and 135 non-obese individuals by an Italian study, which found that age, BMI, waist-hip ratio, blood pressure, insulin and TGs were significantly greater in the Adv36-seropositive group [30].

Additionally, one US study showed that obese and non-obese human participants, who were Adv36 antibody-positive, had lower levels of TG and TC than those who were Adv36 antibody-negative [16]. These associations were also observed in some animal models such as chickens, mice and non-human primates infected with Adv36. Although infection with Adv36 reduces serum TG and TC levels in animal models, this effect in humans is not completely reliable [13]. A study in Korean schoolchildren, reported that within the obese group, the TG level was significantly higher in Adv36 antibody-positive children than those who were Adv36 antibody-negative [19]. Similarly, Adv36 was associated with lower serum lipids, cholesterol, and TGs in humans [16] but, the explanation for this association is still unknown.

A meta-analysis of 10 observational studies demonstrated that Adv36 infection was not associated with abnormal metabolic markers such as TC, high-density lipoprotein cholesterol, TGs, glucose levels, systolic blood pressure and waist circumference. A significant difference was only found in relation to the LDL cholesterol level [34]. However, in our study, some parameters showed similarities. There were no significant differences between TC, TGs and LDL cholesterol when Adv36-positive and -negative obese and non-obese participants were compared. In addition to these parameters, in our study there were no significant differences between TNF-α and IL-6 cytokine levels. On the other hand, a significant difference was detected in the level of leptin. Leptin levels were significantly lower in Adv36-positive obese children and adults than Adv36-negative obese children and adults ($P > 0·05$).

Eventually, we detected a strong relationship between Adv36 seropositivity and obesity in our study as well as other scientific studies. Furthermore, some

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serum lipid parameters partially supported this relationship, although it is not exactly clear if the relationship of lowered leptin levels and positive Adv36 antibody status is linked or associated with different mechanisms. If indeed Adv36 has key a role in human obesity, it may influence obesity treatment or prevention approaches and lead scientists to look for additional adipogenic agents. If Adv36 infection persists long term and continues to maintain obesity in an individual, an effective obesity treatment will have to contain new anti-Adv36 therapeutics. On the other hand, if it is a 'hit-and-run' type of event, at that point a preventive approach, such as vaccination, may be suitable to reduce the risk of obesity. Clearly, such a vaccine may only target specific agents, such as viruses or bacteria, instead of other obesity-contributing factors, in order to eliminate or reduce the current risk. Even this obesity prevention approach could be more effective than some of the current approaches.

CONCLUSION

After taking everything into account, Adv36 is the main virus that studies on experimental animals and humans have shown to be related to the improvement of obesity. The findings are interesting but more research is needed to identify the possible pathogenic mechanisms. Indeed, a large-scale study incorporating various ethnic groups and age groups should be performed to investigate the relationship between Adv36 infection and obesity or related disorders. However, as obesity is a multifactorial disease, it is very difficult to identify in which obese patients infection is the only cause of obesity. Not all patients infected by Adv36 have a relationship with obesity, so it would be useful to know why some of them are protected; an analysis of which genetic factors have a role in this issue is needed. At this stage, molecular and *in vitro* studies should be performed to answer these questions and establish the exact mechanisms of this relationship.

The best solution to improving the health status of obese patients is weight loss, but the aetiology of this complex disease is multifactorial, and a better description of the various aetiological factors is necessary to develop more effective prevention and treatment strategies. The available data on the possible relationship between Adv36 infection and obesity both in children and adults does not completely solve the problem, although Adv36 may be a contributing factor.

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DECLARATION OF INTEREST

None.

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