European Journal of Molecular & Clinical Medicine
ISSN 2515-8260 Volume 08, Issue 1, 2021

Effects of ADIPOQ Gene Polymorphisms on Combined Training - induced Weight Loss of Obese Boys

Aliakbar Jahandideh[1]*, Hamid Rajabi[2], Hadi Rohani[1], Mohammad Shariatzadeh[1]

1. **Aliakbar Jahandideh[1]***
Sport Sciences Research Institute, Tehran, Iran.
* E-mail: aliakbarjahandideh3 @ gmail.com
2. **Hamid Rajabi [2]**
Department of Exercise Physiology, Faculty of Physical Education and Sports Sciences, Kharazmi University, Tehran, Iran.
3. **Hadi Rohani[1]**
Sport Sciences Research Institute, Tehran, Iran.
4. **Mohammad Shariatzadeh[1]**
Sport Sciences Research Institute, Tehran, Iran.

Abstract

The purpose of the present study was to investigate whether the ADIPOQ +276 G>T (rs1501299) and –11377 G>C (rs266729) polymorphisms, would influence the effect of a 8- week Combined Training program. After the pre-test, 30 obese boys (BMIZ>+2), aged 11-13 (12.66±0.47) participated in the combined training protocol for 3 sessions per week for 2 months. DNA was extracted from cheek cells donated by the 30 participants and genotyping was carried out using PCR. Our results suggest that the ADIPOQ genotypes can modulate training-induced body mass measurement changes: After the training program, carriers of rs266729 C allele were characterized by a greater reduction in Fat Mass Percentage (FM), BMIZ, WHR and carriers of rs1501299 G and T by a greater reduction in Body Mass, BMIZ and Fat Mass Percentage and WHR, respectively. Moreover, the ADIPOQ polymorphisms were associated with changes in lipid profile and Adiponectin hormone in response to training. Additionally, we showed two main effects of genotypes (rs266729) for the cholesterol and adiponectin in response to training. From this evidence, it could be concluded that rs266728 G variants may be considered as a disadvantageous factor in the context of training-induced effects on body mass traits in obese boys.

Keywords: Genetics, rs266729, rs1501299, Body mass index, Childhood obesity.

Introduction

Childhood obesity has become a major health concern and occurs at younger ages. Severe obesity in children, especially among young children, is increasing and is expected to continue (Lakshman, Elks, & Ong, 2012). In addition, some of the complications of obesity, such as type 2 diabetes, high blood pressure, and hyperlipidemia that were previously seen only in adults, are now seen in obese children (Lakshman et al., 2012).

Children typically adopt lifestyles, especially poor diet habits, inactive leisure time, and lack of physical activity (PA), which negatively affect their nutritional status. Although diet and lifestyle factors are the main factors influencing obesity, the differential susceptibility to weight gain is also affected by genetic variations (Speakman, 2004). A genetic contribution to the development of obesity has been widely recognized, but the genes involved have not been completely clarified. Some studies demonstrated an association between adipokine single-nucleotide polymorphisms (SNPs) and obesity (Yu et al., 2012).

Adiponectin is an adipokine that is specifically and highly expressed in human adipose tissue (Maeda et al., 1996). The specific gene coding for adiponectin, officially named ADIPOQ, is placed on chromosome 3q27. ADIPOQ includes three exons, spanning a total of 16 KB of genomic sequence

(Passariello et al., 2010). A total of 42 single nucleotide polymorphisms in the gene and its regulatory region with a minor allele frequency of >1.5% have been described (Gu, 2009). Among genetic variants of the ADIPOQ gene, which were described in the context of genetic conditioning for a predisposition to obesity in some ethnic populations, +276 G>T SNP (rs1501299) and –11377 G>C SNP (rs266729) are the most frequently explored polymorphisms associated with serum levels of adiponectin (Leońska-Duniec et al., 2018). Diminished circulating levels of the adiponectin are inversely correlated with obesity, type 2 diabetes mellitus (T2DM), and atherosclerosis (Stenholm et al., 2010). By contrast, the increased adiponectin levels are related to decreased body weight and improved insulin sensitivity (Stenholm et al., 2010). Furthermore, circulating adiponectin levels is also modulated by exercise training (YATAGAI et al., 2003) and diet (Tsuzaki et al., 2009) related to weight loss.

rs1501299 and rs266729 can impact metabolic traits, including total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), as well as Waist-Hip Ratio (WHR) (Enns, Taylor, & Zahradka, 2011). The primary SNP is located at intron 2 and acts as an enhancer. The G allele of rs1501299 is primarily related to lower insulin sensitivity and increased type 2 diabetes mellitus (T2DM) risk, lower adiponectin levels, and increased blood lipids. Conversely, many carriers of T allele have higher adiponectin levels and as a result a lower body mass index (BMI) (Lu et al., 2014). The second polymorphism is located at the 5'-flanking region and also has an influence on the transcription level of the ADIPOQ (Lu et al., 2014). Has been suggested that the G allele of rs266729 is associated with various detrimental conditions, including lower adiponectin levels, risk for developing hypertension, and, in a few cases, the risk of creating colorectal cancer (Ong et al., 2010). On the other hand, the presence of the C allele has also been associated with higher BMI and obesity risk, increased fasting glucose levels and T2DM (Bouatia-Naji et al., 2006).

Few studies have investigated whether the SNPs in ADIPOQ gene impact the effect of lifestyle intervention on obesity-related characteristics (Chung et al., 2009; Enns et al., 2011; Ong et al., 2010). In any case, the studies have reported inconsistent results in terms of population, gender, age, the degree of metabolic risk levels, and gene x physical activity interactions (Chung et al., 2009; Enns et al., 2011). Subsequently, more different intervention studies have been recommended as necessary for recognizing the independent effects of each ADIPOQ genotype on obesity-related traits. In the present study, we examined whether +276 G>T (rs1501299) and –11377 G>C (rs266729) polymorphisms in the ADIPOQ gene would differentially influence the training - induced weight loss of obese boys and whether there was an interaction between genotype and training.

Methods

Study design

Fifty-eight obese boys aged 11-13 years (mean ±SD 12.66 ± 0.47) were recruited from three middle schools in Quchan, Iran. Inclusion criteria for the present study were the following: (a) age from 11-13 years old (b) SDS-BMI>2 (c) stage I and II in the Tanner classification. Sexual maturation was examined using Tanner stages at the beginning of the study by a self-reported questionnaire. . Written instructions and a depiction of pubertal development stages were used as a guide (Marshall & Tanner, 1970). None of these individuals had engaged in regular activity in the previous 2 months. They had no history of any metabolic, diabetes and cardiovascular diseases. Participants were refrained from taking any medications or supplements known to affect metabolism.

Fifty-eight samples were assessed for Adipoq gene variations. Among those, thirty participants were selected based on representing all three genotypes in each polymorphism. For each participant (30 Subjects), blood samples, height and weight, waist-to-hip ratio (WHR) and body mass index for sex/age z-score (BMIz) were measured 48 hours before and after training program. Written informed consent

was obtained from the participants and their parents after they had received a detailed explanation of the study aims and procedures. The study was approved by the Sport Science Research Institute of Iran Research.

Physical exercises, training protocol

Physical exercises were conducted by professional kinesiologists. The training program was three times per week (each session lasted 70 minutes) during 8 weeks. The training program includes 5 minutes of warm up (stretching exercises, light running), 30 minutes of low- intensity rhythmic aerobic movements, 1 set of 7 resistance exercises (dumbbell squat, dumbbell chest press, medicine ball trunk rotation, dumbbell shoulder press, dumbbell bicep curls, band Lat pull-down on the chair and dumbbell lunge). Five minutes of static and stretching exercises were performed to cool down. In order to observe the principle of overload, 5 to 10 percent was added to the number of repetitions or activity time every two weeks.

Blood Analyses

Blood sampling was in two stages: 48 hours before and after 8 weeks of exercise training program. Blood samples were taken after a 12-h overnight fast at 7am from the elbow vein. Blood analyses were performed immediately after the blood collection. Blood samples for biochemical analyses were centrifuged 300 × g for 15 minutes at room temperature in order to receive blood plasma. Blood plasma was used to determine lipid profile levels including: TG, TC, HDL-C, LDL-C (using assay kits from the Pars Azmoon Company, Iran) and adiponectin concentrations (AdipoGen ELISA kits, Korea). All samples were measured in duplicate.

Genetic Analyses

DNA was extracted from Cheek cells of 30 saliva samples using the oragen Company kit. The PCR product of 5'- TTGCCCTGCCTCTGTCTGA-3' (forward) and 5'-GCCTGGAGAACTGGAAGCTG-3' (reverse) for rs266729 and 5'-GACCAGGAAACCACGACTCAAG 3' (forward) and 5'-AGGCACCATCTACACTCATCCT-3' (reverse) for rs1501299 were used. Amplicons of 308 bp were visualized with 1% Agarose gel. In this step, PCR reaction of temperature gradient was used for each pair of primers designed in order to find the best primer annealing temperature. After completing the stopping steps, 3 µl of PCR product to ensure optimal replication on 1% Agarose gel was examined. After identifying the appropriate temperature for all three pairs of PCR synthesized primers of all samples, 2µl of PCR product was brought to 0.1% Agarose gel to confirm the correct replication of the desired fragment. Restriction Fragment Length Polymorphism (RFLP) method was used for determining the genotype of the ADIPOQ gene. Enzymatic digestion at 65 ° C overnight consisted of 1 µl of the enzyme, 3 µl of PCR product, 2 µl of the specific buffer, and 15 µl of deionized water. After enzymatic digestion, the enzyme digestion product was electrophoresed on 12% polyacrylamide gel (PAGE) to observe the cut fragments, and three samples with different genotypes were sent to Sina Codun for sequencing. Then, the digested DNA (ADIPOQ rs266729: 135-115bp C/G, ADIPOQ rs1501299: 227-118 bp G/T) was visualized using a gel documentation system.

Statistical Analysis

The Kolmogorov-Smirnov test of data was used to evaluate the distribution for normality. Allele frequencies were determined by gene counting. To test the influence of ADIPOQ rs266729 and ADIPOQ rs1501299 polymorphisms on training response, the 2 × 3 mixed-design ANOVA test was used followed by Bonferroni's post-hoc. The Hardy-Weinberg equilibrium analysis was evaluated using a chi-square test with one degree of freedom. The level of statistical significance was set at $p < 0.05$. Statistical analysis was carried out with IBM SPSS Statistics for Windows Version 21.0.

Results

Single locus analysis (rs266729)

Changes in the parameters over an 8-week training with respect to the ADIPOQ rs266729 genotype are presented in Table 1. Two way ANOVA for repeated measures revealed a significant effect of training for body mass, BMI, FM, WHR, BMIZ, lipid profile and adiponectin (Table 1).

Table 1: The ADIPOQ rs266729 genotypes and response to training (two-way mixed ANOVA).

Parameter	CC (n = 13)		GC (n = 11)		GG (n = 6)		Two way ANOVA, P-value		
	Pre Training	Post Training	Pre Training	Post Training	Pre Training	Post Training	Genotype	Training	Genotype × Training Interaction
Body Mass (kg)	77.94 ±10.06	75.99 ±10.52	81.05 ±6.11	77.9 ±6.4	76.33 ±17.68	75.92 ±17.88	0.79	<0.01*	0.1
FM (%)	33.93 ±4.23	30.98 ±4.84	31.36 ±4.2	29.54 ±4.78	34 ±3.39	33.45 ±3.68	0.08	<0.01*	0.08
BMIZ	2.16 ±0.12	2.10 ±0.17	2.1 ±0.11	2 ± 0.15	2.11 ±0.15	2.12 ±0.014	0.36	<0.01*	0.1
WHR	0.93 ±0.05	207.61 ±33.87	0.94 ± 0.25	0.92 ±0.031	0.98 ±0.041	0.98 ±0.045	0.05	<0.01*	0.12
TG (mg/dl)	207.61 ±33.87	183.76 ±32.85	181.45 ±42.81	160.63 ±34.05	196.6 ±16.08	182.6 ±18.77	0.14	<0.01*	0.77
HDL-C (mg/dl)	38.84 ±4.77	43.15 ±4.59	41.9 ±4.25	45.90 ±5.53	38.7 ±2.38	39.5 ±1.7	0.05	<0.01*	0.019
LDL-C (mg/dl)	117.61 ±30.6	100.23 ±30.06	96.18 ±31.99	90.09 ±25.95	106 ±23.73	100.16 ±17.76	0.35	<0.01*	0.18
TC (mg/dl)	205.2 ±34.57	172.3 ±35.25	176.8 ±42.43	170.54 ±33.23	195.5 ±19.14	191.5 ±20.1	0.38	<0.01*	0.011*
Adiponectin (ng/ml)	9.56 ±1.19	11.67 ±1.77	10.84 ±1.28	12.36 ±1.44	10.59 ±1.32	10.33 ±0.73	0.81	<0.01*	0.012*

Values are presented as mean ± standard deviation; BMI: Body Mass Index; FM: Body Fat Percentage; WHR: waist to hip ratio; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol.

P-value significantly different (P<0.05).

In addition, there were 2 genotype × training interactions. After training program, CC homozygote (9.56 ± 1.19 vs 11.67 ± 1.77) had significantly higher adiponectin than GG carriers (P = 0.01; F = 5.19), (Table 1, Figure 1). Also, There was a significant interaction training × ADIPOQ rs266729 genotype for TC (F=5.39, p=0.011), (Table 1, Figure 1). A training-related change (decrease) in plasma TC concentration in the ADIPOQ rs266729 CC heterozygotes differed significantly from the change in the TG (p=0.024) and GG homozygotes (p=0.047) homozygotes (Figure 1). The positive effect of training on other lipid profile markers was observed in carriers of C allele, although not significant (Table 1).

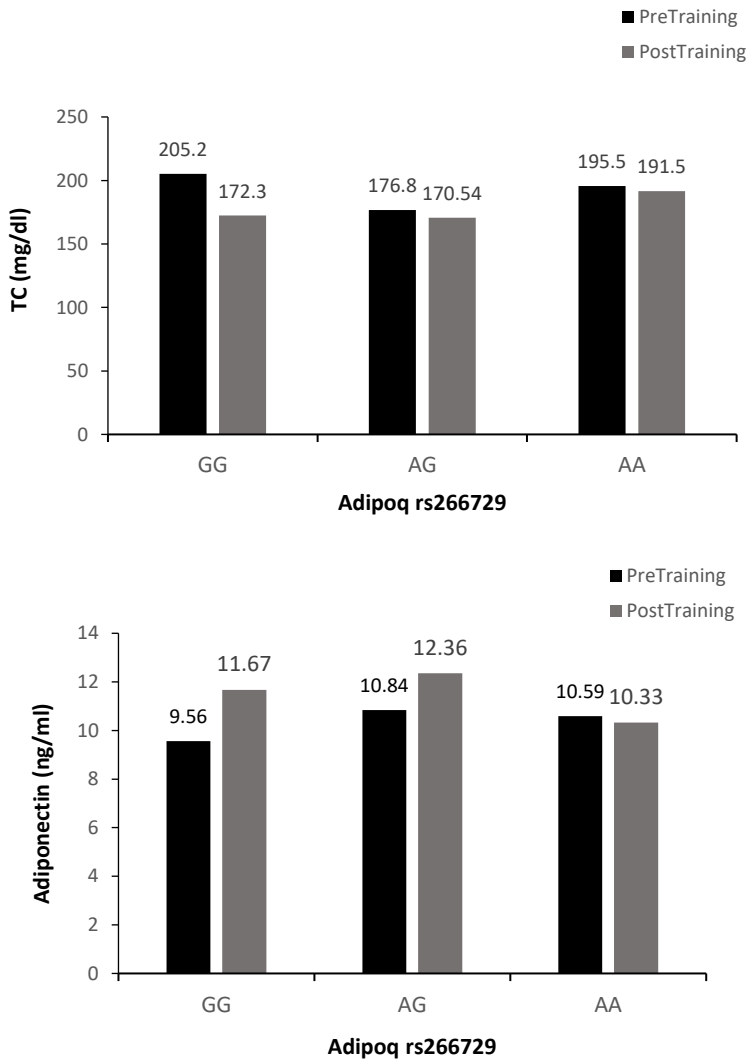

Figure 1. Training × genotype ADIPOQ rs266729 interaction for TC and Adiponectin level (mean±SD)

Single locus analysis (rs1501299)

Changes in the parameters over an 8-week training with respect to the ADIPOQ rs1501299 genotype are presented in Table 1. Two way ANOVA for repeated measures revealed a significant effect of training for body mass, BMI, FM, Whr, BMIZ, lipid profile and adiponectin (Table 2). However, no significant effect of genotype on changes in measured parameters was observed after 8 weeks of training (genotype × training).

Table 2: The ADIPOQ rs1501299 genotypes and response to training (two-way mixed ANOVA).

Parameter	GG (n = 17)		TG (n = 8)		TT (n = 5)		Two way ANOVA, P-value		
	Pre Training	Post Training	Pre Training	Post Training	Pre Training	Post Training	Genotype	Training	Genotype × Training Interaction
Body Mass (kg)	76.91 ±9.3	74.25 ±9.65	80.42 ±13.91	79.02 ±14.26	82.42 ±9.57	81.16 ±8.38	0.44	<0.01*	0.38

FM (%)	32.55 ±4.67	30.32 ± 5.21	33.08 ±3.47	31.96 ±3.74	34.38 ±5.06	31.45 ±4.73	0.74	<0.01*	0.33
BMIZ	2.09 ± 0.87	2.01 ± 0.15	2.15 ±0.15	2.11 ±0.15	2.24 ±0.15	2.21 ±0.12	0.03*	<0.02*	0.06
WHR	0.94 ± 0.04	0.93 ± 0.05	0.96 ±0.03	0.95 ±0.03	0.96 ±0.03	0.94 ±0.38	0.49	<0.01*	0.38
TG (mg/dl)	195.7 ± 32.67	165.41 ± 26.27	189.5 ±52.48	181.37 ±39.36	206.4 ±50.47	197.8 ±29.83	0.41	<0.01*	0.73
HDL-C (mg/dl)	40.5 ±3.89	43.05 ±4.26	39.5 ±4.57	45.87 ±6.12	38.8 ±5.8	40.8 ±4.96	0.50	0.01*	0.61
LDL-C (mg/dl)	103.7 ±27.12	92.76 ±23.63	105.25 ±24.68	94 ±23.7	123.6 ±42.7	113.2 ±36.46	0.32	<0.01*	0.99
TC (mg/dl)	189.52 ±31.97	169 ±33.02	189.62 ±40.26	180.62 ±33.03	209.4 ±49.26	189.4 ±27.1	0.47	<0.05	0.58
Adiponectin (ng/ml)	10.47 ±1.13	12.17 ±1.47	9.90 ±1.41	11.28 ±1.45	9.98 ±2.01	10.48 ±1.92	0.14	<0.01*	0.38

Values are presented as mean ± standard deviation; BMI: Body Mass Index; FM: Body Fat Percentage; WHR: waist to hip ratio; TC: Total Cholesterol; TG: Triglycerides; HDL-C: High-Density Lipoprotein Cholesterol; LDL-C: Low-Density Lipoprotein Cholesterol.
P-value significantly different (P<0.05).

Discussion

Many studies have tried to find the association between genes and obesity-related traits; nevertheless, there is little knowledge about the lifestyle × adiponectin gene interactions, and the findings are conflicting. In the present study, the differences in the effects of polymorphism rs266729 (-11377 G>C) and rs1501299 (+276 G>T) of adiponectin gene on the obesity-related traits, lipid profile and adiponectin hormone in obese boys were examined.

After the training program, the highest decrease in body mass was observed in CG genotype and the highest decrease in body fat percentage in CC genotype of rs266729 compared to GG genotype. In addition, after the training program, the lipid profile also changed, so that the greatest decrease in TG, TC, LDL-C and an increase in HDL-C was observed in the C allele of rs266729 polymorphism. On the other hand, our results indicated two main effects of genotype for TC and adiponectin, so that C allele carriers in response to 8 weeks of training, significantly reduced TC and increased adiponectin. Previous researchers have revealed that the G allele of rs266729 polymorphism was mainly associated with lower levels of adiponectin, a higher amount of lipid profile, and consequently identified G allele as a risk factor (Leońska-Duniec et al., 2018) that is in line with the results of our study. In obese individuals, adiponectin levels are lower and may be attributed to blood fat disorders (Kim et al., 2007), and in most studies reporting that training enhances adiponectin levels, it has been associated with a significant reduction in fat mass (Oberbach et al., 2006). Some results have suggested that training could increase adiponectin concentrations during weight loss programs and there is a strong association between plasma levels of adiponectin and fat metabolism (Balagopal, George, Yarandi, Funanage, & Bayne, 2005; Kazemi, Rahmati, Eskandari, & Taherabadi, 2016). Balagopal et al (21) and kazemi et al (Kazemi et al., 2016) have reported that aerobic training increases adiponectin and reduces fat mass. Furthermore, it has been indicated that 6 weeks of training enhance the adiponectin levels by 10%, along with reducing the fat mass weight, TG, and insulin levels.

Adiponectin has been found to be correlated with different parameters of lipoprotein metabolism and, particularly, it is related to the metabolism of HDL-C and TG. Adiponectin shows up to actuate an increment in serum HDL and, in addition, it brings down serum TG through the improved catabolism of TG-rich lipoproteins (Christou & Kiortsis, 2013). Almost all of the previous studies reported that serum adiponectin is emphatically related with serum HDL-C level (Yanai & Yoshida, 2019). Adiponectin through an increment within the generation of ATP-binding cassette transporter A1 (ABCA1), which actuates HDL-C get together through reverse Cholesterol transport (Yanai & Yoshida, 2019). Another possible mechanism underlying the adiponectin-induced up-regulation of HDL-C is the activation of lipoprotein lipase (LPL) by adiponectin and/or the advancement of insulin resistance, which can also diminish TG (Yanai & Yoshida, 2019). The majority of previous studies have illustrated a negative association between circulating adiponectin and serum TG (Clarenbach et al., 2007; Kangas-Kontio et al., 2010). A conceivable clarification for the adiponectin-induced increase in TG catabolism is the control of LPL activity by adiponectin. It is well known that LPL, which is translocated to the endothelial cell surface of the vessels of the heart, muscles, and adipose tissue, hydrolyses TG in TG-rich lipoproteins including chylomicrons and VLDL (Yanai & Yoshida, 2019). Subsequently, adiponectin may have a direct role in inducing LPL expression and activation in both skeletal muscle and adipose tissue (Yanai & Yoshida, 2019). Another possible mechanism for TG reduction by adiponectin would be attributable to adiponectin-induced diminish in serum Apolipoprotein C-III (APO-CIII), a well-known inhibitor of LPL, as shown by the reported negative association between circulating adiponectin and serum APO-CIII. (Tsubakio-Yamamoto et al., 2012).

A further increase in adiponectin levels in CC genotypes in our study was associated with a further decrease in the levels of TG, TC, LDL-C, and an increase in HDL-C, supporting a more protective role of adiponectin. Moreover, changes in allele G of rs266729 genotype may be considered as an inappropriate factor in the effects of an exercise program in obese boys with body mass and lipid profile; however, further research is needed.

In the rs1501299 genotype, no significant change was seen in the studied variables in response to combined training. Nevertheless, carriers of allele G showed a greater decrease in body mass and, BMIZ, TG and a greater increase in HDL-c and adiponectin levels. On the contrary, carriers of allele T had a greater decrease in body fat percentage and WHR. Leońska-Duniec et al. (Leońska-Duniec et al., 2018) previously argued that after a 12-week aerobic training program in healthy young women, TT allele carriers experienced a greater decrease in body mass and body fat percentage compared to TG and GG allele carriers. Furthermore, Huang et al. (Huang et al., 2007) indicated that in response to aerobic training, people with TT+GT genotype (rs1501299) showed more adiponectin compared to GG in response to training, which is not in line with our study. Some studies have previously shown that the G allele of rs1501299 genotype is mainly associated with greater reduction levels of adiponectin, BMI, lipid profile; therefore, they have considered G allele as a risk factor, in contrast to carriers of T allele had higher adiponectin and lower BMI levels (Huang et al., 2007; Passariello et al., 2010). On the other hand, some other researchers, such as De Luis et al. (de Luis et al., 2019), Bouatia-Naji (Bouatia-Naji et al., 2006) and Beebe-Dimmer (Beebe-Dimmer, Zuhlke, Ray, Lange, & Cooney, 2010), considered T allele as a risk factor, stating that the presence of T allele has been seen with obesity-related traits. Although our study was not aimed at investigating this relationship, rs1501299 has been examined in many populations such as American, Asian, and European (Gable, Hurel, & Humphries, 2006) and there has been instability among the studies. It should be considered that these studies have used various African-American (Beebe-Dimmer et al., 2010), French (Bouatia-Naji et al., 2006), Polish (Leońska-Duniec et al., 2018), Caucasian, Asian populations with various gender, BMI, and age; as indicated in a meta-analysis of 54 studies, rs1501299 is associated only with obesity in Caucasian ethnicity, and not in Asian ethnicity (Lu et al., 2014). Besides, most studies have been conducted on

adults, and the results may show that adults have more metabolic flexibility in producing and secreting adiponectin in response to training and weight loss. Consequently, a more diverse interventional study is needed to identify the independent effects of ADIPOQ genotype (rs150129) on obesity-related traits.

Conclusions

Our results obviously indicate that the C allele of the adiponectin gene (rs266729) may improve the positive effects of combined training on obesity-related traits such as body fat percentage and lipid profile. Hence, from this evidence, it could be concluded that rs266729 G variants may be considered as a disadvantageous factor in the context of training-induced effects obesity-related traits, lipid profile, as well as adiponectin levels in obese boys. Further studies are required to analyze this ambiguous subject.

Conflict of interest

The authors declare no conflict of interest

Reference

1. Balagopal, P., George, D., Yarandi, H., Funanage, V., & Bayne, E. (2005). Reversal of obesity-related hypoadiponectinemia by lifestyle intervention: a controlled, randomized study in obese adolescents. The Journal of Clinical Endocrinology & Metabolism, 90(11), 6192-6197.

2. Beebe-Dimmer, J. L., Zuhlke, K. A., Ray, A. M., Lange, E. M., & Cooney, K. A. (2010). Genetic variation in adiponectin (ADIPOQ) and the type 1 receptor (ADIPOR1), obesity and prostate cancer in African Americans. Prostate Cancer and Prostatic Diseases, 13(4), 362-368.

3. Bouatia-Naji, N., Meyre, D., Lobbens, S., Séron, K., Fumeron, F., Balkau, B., . . . Dina, C. (2006). ACDC/adiponectin polymorphisms are associated with severe childhood and adult obesity. Diabetes, 55(2), 545-550.

4. Christou, G., & Kiortsis, D. (2013). Adiponectin and lipoprotein metabolism. Obesity reviews, 14(12), 939-949.

5. Chung, H. K., Chae, J. S., Hyun, Y. J., Paik, J. K., Kim, J. Y., Jang, Y., . . . Lee, J. H. (2009). Influence of adiponectin gene polymorphisms on adiponectin level and insulin resistance index in response to dietary intervention in overweight-obese patients with impaired fasting glucose or newly diagnosed type 2 diabetes. Diabetes care, 32(4), 552-558.

6. Clarenbach, J. J., Vega, G. L., Adams-Huet, B., Considine, R. V., Ricks, M., & Sumner, A. E. (2007). Variability in postheparin hepatic lipase activity is associated with plasma adiponectin levels in African Americans. Journal of Investigative Medicine, 55(4), 187-194.

7. de Luis, D. A., Izaola, O., Primo, D., Gómez-Hoyos, E., Ortola, A., López-Gómez, J. J., & Aller, R. (2019). Role of rs1501299 variant in the adiponectin gene on total adiponectin levels, insulin resistance and weight loss after a Mediterranean hypocaloric diet. Diabetes research and clinical practice, 148, 262-267.

8. Enns, J. E., Taylor, C. G., & Zahradka, P. (2011). Variations in adipokine genes AdipoQ, Lep, and LepR are associated with risk for obesity-related metabolic disease: the modulatory role of gene-nutrient interactions. Journal of obesity, 2011.

9. Gable, D., Hurel, S., & Humphries, S. (2006). Adiponectin and its gene variants as risk factors for insulin resistance, the metabolic syndrome and cardiovascular disease. Atherosclerosis, 188(2), 231-244.

10. Gu, H. F. (2009). Biomarkers of adiponectin: plasma protein variation and genomic DNA polymorphisms. Biomarker Insights, 4, BMI. S3453.

11. Huang, H., Iida, K. T., Murakami, H., Saito, Y., Otsuki, T., Iemitsu, M., . . . Ajisaka, R. (2007). Influence of adiponectin gene polymorphism SNP276 (G/T) on adiponectin in response to exercise training. Endocrine journal, 54(6), 879-886.

12. Kangas-Kontio, T., Huotari, A., Ruotsalainen, H., Herzig, K.-H., Tamminen, M., Ala-Korpela, M., . . . Kakko, S. (2010). Genetic and environmental determinants of total and high-molecular weight adiponectin in families with low HDL-cholesterol and early onset coronary heart disease. Atherosclerosis, 210(2), 479-485.

13. Kazemi, A., Rahmati, M., Eskandari, F., & Taherabadi, S. J. (2016). Effect of 8 weeks sprint interval training on serum levels of Adiponectin and insulin in overweight children. ISMJ, 19(1), 37-47.

14. Kim, E. S., Im, J. A., Kim, K. C., Park, J. H., Suh, S. H., Kang, E. S., . . . Yoon, Y. J. (2007). Improved insulin sensitivity and adiponectin level after exercise training in obese Korean youth. Obesity, 15(12), 3023-3030.

15. Lakshman, R., Elks, C. E., & Ong, K. K. (2012). Childhood obesity. Circulation, 126(14), 1770-1779.

16. Leońska-Duniec, A., Grzywacz, A., Jastrzębski, Z., Jażdżewska, A., Lulińska-Kuklik, E., Moska, W., . . . Dornowski, M. (2018). ADIPOQ polymorphisms are associated with changes in obesity-related traits in response to aerobic training programme in women. Biology of sport, 35(2), 165.

17. Lu, J.-f., Zhou, Y., Huang, G.-h., Jiang, H.-x., Hu, B.-l., & Qin, S.-y. (2014). Association of ADIPOQ polymorphisms with obesity risk: a meta-analysis. Human immunology, 75(10), 1062-1068.

18. Maeda, K., Okubo, K., Shimomura, I., Funahashi, T., Matsuzawa, Y., & Matsubara, K. (1996). cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPoseMost abundant Gene transcript 1). Biochemical and biophysical research communications, 221(2), 286-289.

19. Marshall, W. A., & Tanner, J. M. (1970). Variations in the pattern of pubertal changes in boys. Arch Dis Child, 45(239), 13-23. doi:10.1136/adc.45.239.13

20. Oberbach, A., Tönjes, A., Klöting, N., Fasshauer, M., Kratzsch, J. r., Busse, M. W., . . . Blüher, M. (2006). Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. European Journal of Endocrinology, 154(4), 577-585.

21. Ong, K. L., Li, M., Tso, A. W., Xu, A., Cherny, S. S., Sham, P. C., . . . Lam, K. S. (2010). Association of genetic variants in the adiponectin gene with adiponectin level and hypertension in Hong Kong Chinese. European Journal of Endocrinology, 163(2), 251.

22. Passariello, C. L., Gruodytė, R., Hiio, K., Mäestu, J., Jürimäe, J., Saar, M., . . . Jürimäe, T. (2010). ADIPOQ SNP45 associated with lean body mass in physically active normal weight adolescent girls. American Journal of Human Biology, 22(6), 813-818.

23. Speakman, J. R. (2004). Obesity: the integrated roles of environment and genetics. The Journal of nutrition, 134(8), 2090S-2105S.

24. Stenholm, S., Koster, A., Alley, D. E., Visser, M., Maggio, M., Harris, T. B., . . . Ferrucci, L. (2010). Adipocytokines and the metabolic syndrome among older persons with and without obesity: the InCHIANTI study. Clinical endocrinology, 73(1), 55-65.

25. Tsubakio-Yamamoto, K., Sugimoto, T., Nishida, M., Okano, R., Monden, Y., Kitazume-Taneike, R., . . . Yuasa-Kawase, M. (2012). Serum adiponectin level is correlated with the size of HDL and LDL particles determined by high performance liquid chromatography. Metabolism, 61(12), 1763-1770.

26. Tsuzaki, K., Kotani, K., Nagai, N., Saiga, K., Sano, Y., Hamada, T., . . . Horikawa, C. (2009). Adiponectin gene single-nucleotide polymorphisms and treatment response to obesity. Journal of endocrinological investigation, 32(5), 395-400.

27. Yanai, H., & Yoshida, H. (2019). Beneficial effects of adiponectin on glucose and lipid metabolism and atherosclerotic progression: mechanisms and perspectives. International journal of molecular sciences, 20(5), 1190.

28. Yatagai, T., Nishida, Y., Nagasaka, S., Nakamura, T., Tokuyama, K., Shindo, M., . . . Ishibashi, S. (2003). Relationship between exercise training-induced increase in insulin sensitivity and adiponectinemia in healthy men. Endocrine journal, 50(2), 233-238.

29. Yu, Z., Han, S., Cao, X., Zhu, C., Wang, X., & Guo, X. (2012). Genetic polymorphisms in adipokine genes and the risk of obesity: a systematic review and meta-analysis. Obesity, 20(2), 396-406.