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LEP and LEPR polymorphisms influences anthropometric outcome in response to 8 weeks of combined training in obese boys

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Abstract

Objective The purpose of the present study was to investigate whether *LEP19 G>A* and *LEPR 668 A>G* polymorphisms would influence the effect of an 8-week combined aerobic and resistance training.

Methods Thirty obese boys (BMIz>+2) aged 11–13 (12.66±0.47) years were recruited from three middle schools in Quchan. The changes in body composition parameters and metabolic factors in response to 8-weeks combined aerobic and resistance training program were analyzed regarding *LEP* and *LEPR* polymorphism. DNA was extracted from cheek cells donated by the 30 participants and genotyping was carried out using PCR.

Results Our results suggest that carriers of *rs2167270G* and *rs1137101A* allele were characterized by a greater reduction in body mass and waist-to-hip ratio (WHR) (P<0.05). Also, a significant decrease was observed in leptin levels in carriers of *rs2167270G* allele after the training program (P=0.031). Moreover, the LEP and LEPR polymorphisms were associated with changes in lipid profile in response to training.

Conclusions In response to 8 weeks of regular physical activity, obese boys with G (*rs2167270*) and A (*rs1137101*) alleles had the best likelihood of losing weight which was associated with a decrease in body mass, fat mass (%), WHR and leptin concentrations.

Keywords Body mass index, Health promotion, Physical activity, Genetic, Boy

Introduction

Childhood obesity is one of the major public health challenges, raising concerns for developing serious health conditions.[1,2] Studies in developing countries and the Middle East show an increase in childhood obesity and its growing trend.[3, 4] Comparative patterns have been observed in Iranian children, with 7–12% obesity rate, reported in children aged 6–12 years.[5] According to a nationwide study in Iran, overall prevalence of elevated body mass index (BMI), including obesity and overweight in children and adolescents has increased over the years.[6] Potential contributors of increased obesity includes genetic factors, increased energy intake, physical inactivity, environmental, social and psychological factors, neurological disorders, and overeating in childhood.[4]

Obesity has a strong genetic basis, and numerous genetic variants have been associated with its phenotypes.[7] Genome-wide association studies (GWAS) have identified several genetic variants that are related with BMI and obesity in adulthood.[8] In 2007, the first BMI locus was found in the fat mass and obesity-associated (*FTO*) locus, taken after by Melanocortin 4 receptor (*MC4R*) in 2008, and 18 further loci in 2010.[9] While the focus of these studies has been on BMI or obesity in adult populations, reports have showed that some of these genetic variations are also significant associations with childhood BMI.[9]

Leptin gene (*LEP*) and leptin receptor gene (*LEPR*) are commonly studied genes in the field of obesity. Several common polymorphisms of both *LEP* and *LEPR* genes (located on chromosome 7q31and 1p31, respectively) have been studied in various populations for their potential association with the development of human obesity and its related complications.[10, 11] Among these single nucleotide polymorphisms (SNPs), the *LEP A19G* polymorphism (*rs2167270*) of the untranslated region of exon 1 affects leptin concentration and has been investigated in detail for its effects on obesity-related metabolic disease.[12] Some studies indicate that the A allele is associated with higher leptin levels and lower BMI[13] and it could be concluded that the G variant may be considered a disadvantageous factor in the context of obesity-related traits.[14] Variants of *LEPR* have also been described to influence leptin receptor activity.[12] The first to identify was a SNP in the coding region of the leptin receptor gene, *GLN223ARG*.[15] The *GLN223ARG* polymorphism, characterized by an adenine (A) to guanine (G) transition at position 668 (codon 223) in exon 6 in the extracellular domain of *LEPR* results in an amino acid substitution (glutamine with an arginine). This substitution of amino acid glutamine (GLN) to arginine (ARG) occurs in the intracellular domain of the receptor.[16] It has been suggested that the change of GLN by an ARG causes a change of electric charge from neutral to positive within the protein, which can affect the functional characteristics of the receptor. This seems to be associated with an impaired signaling capacity of the leptin receptor and with higher mean circulating level of leptin.[17] The G allele has mainly been connected with increased adiposity, BMI, percent fat mass (% FM), as well as higher circulating insulin and leptin levels.[14] But, the results obtained so far are ambiguous. Some studies suggested no association between G allele and obesity-related parameters, while the others found the association with a lean phenotype.[18, 19] On the other hand, the A allele has also been found to be associated with total abdominal fat mass, increased insulin and leptin levels, and higher risk of developing type 2 diabetes.[20] Not all the studies have demonstrated the association between the polymorphisms and obesity.[12]

Previous studies showed genetics factors can affect body responses to weight loss programs.[21, 22] However, few studies evaluated the impact of polymorphisms on metabolic

parameters changes during weight loss, especially in children.[23] Therefore, considering that combined aerobic and resistance training has been proposed as an interesting training strategy for maintaining and/or improving health and seems to be an effective strategy for preventing and managing obesity.[24] Therefore, the aim of our study is to investigate the effect of SNPs in *LEP* (*rs2167270*) and *LEPR* (*rs1137101*) on metabolic response and weight loss after 8-weeks of combined training in obese children boys.

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 to 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.[25] 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 *LEP* and *LEPR* gene variations. Among those, 30 participants were selected based on representing all three genotypes in each polymorphism (AA, AG, and GG for *LEP* and AA, GA, and GG for *LEPR*). 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 h 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 (IR.SSRC.REC.1299.111).

Physical exercise training protocol

Physical exercises were supervised by professional kinesiologists. Training program was three times per week (each session lasted 70 min) during 8 weeks. Training program includes 5 min of warm-up (stretching exercises, light running), 30 min of low-intensity rhythmic aerobic movements, 1 set of 7 resistance exercises (dumbbell squat, dumbbells chest press, medicine ball trunk rotation, dumbbell shoulder press, dumbbell bicep curl, 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, 5–10 percent was added to the number of repetitions or activity time every 2 weeks.

Blood analyses

Blood sampling was at two stages: 48 h before and after 8 weeks of exercise training program. Blood samples were taken after a 12-h overnight fast at 7 am from the elbow vein. Blood samples for biochemical analyses were centrifuged 300 × g for 15 min at room temperature in order to receive blood plasma. Blood plasma was used to determine lipid profile levels including: triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) (using assay kits from Pars Azmoon Company, Iran), and leptin concentrations (Mecrodia ELISA kits, Sweden). All samples were measured in duplicate.

Genetic analyses

Participants were asked to refrain from eating or drinking 30 min prior to saliva collection. Each individual was instructed to rub their tongues around the inside of their mouths for about 30 sec, and then expectorate approximately 2 ml saliva into the tube. DNA was extracted from Cheek cells of 58 saliva samples using the Oragen Company kit. The PCR product of 5'-CAGTTGCGCAAGTTGTGATCG-3' (forward) and 5'-GCTGGTTCTGCAAGGTCCTG-3' (reverse) for *rs2167270* and 5' GAATGTCTTGTGCCTGTGCCA-3' (forward) and 5'-GAAGCCACTCTTAATACCCCCAGT-3' (reverse) for *rs1137101* were used. Amplicons of 308 bp were visualized with 1% Agarose gel. In this step, PCR reaction of temperature gradient was used for each pairs 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, 2 µl of PCR product was brought to 0.1% Agarose gel to confirm the correct replication of the desired fragment. Restriction fragment length polymorphism method was used for determining the genotype of the *Lep* and *Lepr* genes. 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 to observe the cut fragments, and three samples with different genotypes were sent to Sina Codun for sequencing. Then, the digested DNA (*LEP rs2167270*: 330 (252-77) G/A, *LEPR rs1137101*: 274 (189-85) A/G) 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 the *LEP A19G (rs2167270*) and *LEPR A66G* (*rs1137101*) polymorphisms on training response, two way mixed analysis of variance (ANOVA) was used with genotype as between subject factor and training program as within subject factor. Follow-up verification was made with the Bonferroni post hoc test. 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

LEP A19G (rs2167270) and LEPR A66G (rs1137101) polymorphisms

Both polymorphisms conformed to Hardy–Weinberg expectations (chi-square = 0.5776, P = 0633; chi-square = 0.465, P = 0.55, for the *LEP rs2167270* and *LEPR rs1137101*, respectively). Two-way mixed ANOVA revealed a significant effect of the *LEP* rs2167270 genotype for WHR (Sig = 0.0.34, F = 3.831); nevertheless, no significant effect of *LEPR rs1137101* genotype was observed on measurement variables (Tables 1, 2).

Table 1. **The LEP rs2167270 genotypes and response to training (two-way mixed ANOVA).**

Parameter	GG (n = 13)		AG (n = 12)		AA (n = 5)		Two way mixed ANOVA P-value		
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training	Genotype	Training	Genotype × Training interaction
Body mass (kg)	77.6 ± 7.58	74.2 ± 7.7	76.4 ± 10.2	75.1 ± 10.2	87.1 ± 15.6	86.4 ± 15.3	0.1	<0.01*	0.032*
FM (%)	32.1 ± 4.7	29.3 ± 4.7	33.3 ± 4.07	31.4 ± 4.7	34.3 ± 2.6	33.6 ± 3.1	0.32	<0.01*	0.15
BMIZ	2.13 ± 0.12	2.02 ± 0.15	2.1 ± 0.09	2.06 ± 0.15	2.22 ± 0.17	2.21 ± 0.15	0.13	<0.01*	0.008*
WHR	0.93 ± 0.03	0.91 ± 0.04	0.95 ± 0.02	0.95 ± 0.03	0.98 ± 0.05	0.98 ± 0.04	0.034*	<0.01*	0.049*
TG (mg/dl)	196.61 ± 42.4	182.84 ± 34.7	192.66 ± 35.7	164.16 ± 32.6	201.4± 19.35	181 ± 18.47	0.61	<0.01*	0.41
HDL-C (mg/dl)	40.46 ± 4.75	45.07 ± 5.54	39.71 ± 4.59	42 ± 4.8	39.2 ± 3.11	42.6 ± 3.57	0.09	0.093	0.059
LDL-C (mg/dl)	105.07 ± 31	97.84 ± 30.3	108.58 ± 33.4	96.75 ± 27.6	110.8 ± 14.6	92.4 ± 9.07	0.99	<0.01*	0.44
TC (mg/dl)	198.07 ± 40.8	179.92 ± 33.3	188.16 ± 38.6	168.66 ± 34.8	190.6 ± 22.1	180.4 ± 23.7	0.72	<0.01*	0.8
Leptin (ng/ml)	13.17 ± 1.42	11.09 ± 1.83	13.62 ± 1.61	11.71 ± 1.57	14.11 ± 1.41	13.53 ± 1.44	0.12	<0.01*	0.03*

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. NS: not significant; P-value significantly different (P<0.05).

Table 2. The LEPR rs1137101 genotypes and response to training (two-way mixed ANOVA).

Parameter	AA (n = 10)		GA (n = 13)		GG (n = 7)		Two way mixed ANOVA P-value		
	Pre-training	Post-training	Pre-training	Post-training	Pre-training	Post-training	Genotype	Training	Genotype × Training interaction
Body mass (kg)	82.07 ± 11.6	78.43 ± 12.83	77.5 ± 9.03	75.7 ± 9.09	76.4 ± 12.12	75.69 ± 12.1	0.66	<0.01*	0.04*
FM (%)	32.96 ± 4.14	30.25 ± 5.42	32.02 ± 4.24	31.4 ± 4.7	34.88 ± 3.84	33.44 ± 3.85	0.28	<0.01*	0.5
BMIZ	2.17 ± 0.14	2.06 ± 0.21	2.13 ± 0.12	2.07 ± 0.13	2.09 ± 0.91	2.08 ± 0.14	0.93	<0.01*	0.06
WHR	0.95 ± 0.54	0.93 ± 0.06	0.95 ± 0.03	0.94 ± 0.04	0.95 ± 0.02	0.95 ± 0.02	0.95	<0.01*	0.03*
TG (mg/dl)	196.1 ± 29.39	172 ± 33.07	192.46 ± 45.32	180.38 ± 31.34	201.7 ± 27.87	169.57 ± 35.65	0.98	<0.01*	0.26
HDL-C (mg/dl)	40.3 ± 3.52	43.6 ± 5.98	42.3 ± 3.72	43.76 ± 4.18	39.65 ± 4.57	40 ± 5.44	0.22	0.07	0.44
LDL-C (mg/dl)	105.4 ± 28.22	92.2 ± 17.05	106.07 ± 29.68	101.9 ± 28.02	112.85 ± 33.92	95.42 ± 34.26	0.84	<0.01*	0.14
TC (mg/dl)	193.7 ± 33.57	175.1 ± 37.65	191.3 ± 41.67	180.84 ± 24.95	194.57 ± 36.52	166.14 ± 38.2	0.93	<0.01*	0.34
Leptin (ng/ml)	13.74 ± 1.29	11.74 ± 1.21	12.97 ± 1.58	11.26 ± 2.18	14.17 ± 1.39	12.65 ± 1.74	0.2	<0.01*	0.68

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. NS: not significant; P-value significantly different (P<0.05).

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. NS: not significant; P-value significantly different (P<0.05).

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. NS: not significant; P-value significantly different (P<0.05).

There was a significant effect of interaction between training × genotypes (*rs2167270*) on body mass (P = 0.032, F = 3.934), WHR (P = 0.049, F = 3.38) and leptin hormone (P = 0.031, F = 3.95). Reduction in the GG allele in response to training was greater than the other two alleles (AG and AA) (Fig. 1, Table 1). Furthermore, there was a significant effect interaction between training × *rs1137101* leptin receptor gene on body mass (P = 0.04, F = 3.625) and WHR (P = 0.037, F = 3.75). As opposed to AG and GG, AA homozygotes demonstrated a training-related greater reduction in body mass and WHR (Fig. 2, Table 2). We observed positive effect of training on the other lipid profile markers in carriers of different alleles, although it was not significant (Tables 1, 2).

Discussion

Lifestyle interventions, including increased physical activity, are recommended as an effective treatment for weight loss as well as to improve biochemical parameters in obese boys and adolescents.[26] Our genetic study was designed to test whether variation in the *LEP* and *LEPR* genes can modulate changes in selected body mass, body composition, and leptin hormone following 8 weeks of supervised combined training in obese boys. An important finding of this study was the significant interaction between training and *the LEP rs2167270* genotype for body mass, BMIz, WHR, and leptin level. We also find a significant interaction between training and the *LEPR rs1137101* genotype for body mass and WHR. A training-related decrease in the *LEP* GG and *LEPR* AA homozygotes differed significantly from the change in other alleles. Therefore, the results of our study support the assumption that *LEP* and *LEPR* genes variation play an important role in inter-individual changes of body mass, fat mass, lipid profile, and leptin hormone in response to regular physical activity.

Given the important role of leptin in the regulation of energy metabolism, we suggest that genetic variants of *LEP* and *LEPR* may modulate physiological responses to lifestyle interventions and its influence on health in pre-pubertal obese boys. When analyzed separately, lowest leptin levels were observed in people with G homozygous (*rs2167270*) at

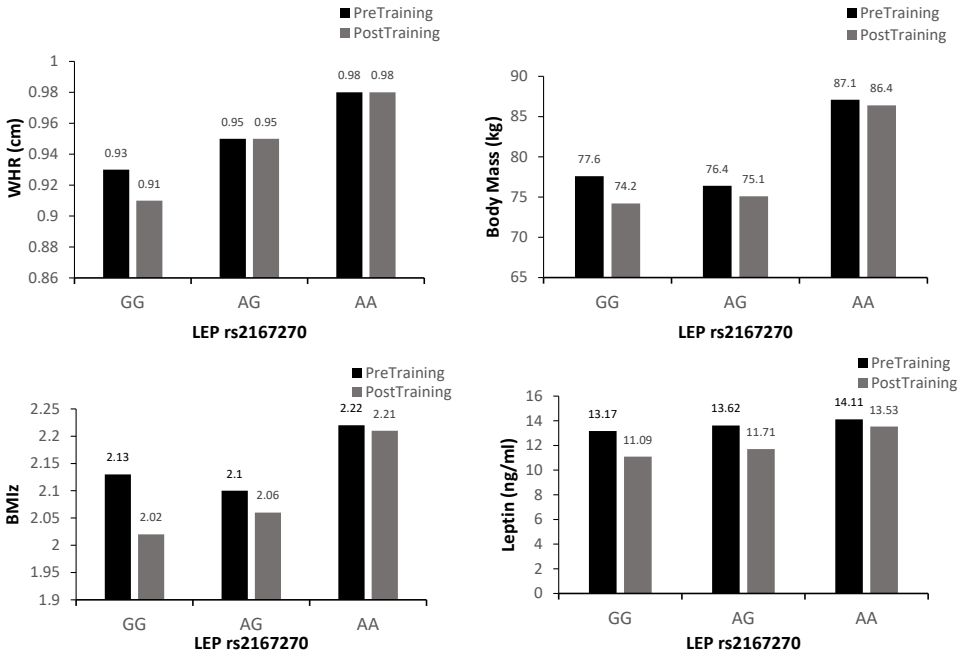

Fig. 1 **Training × genotype LEP rs2167270 interaction for Body Mass, BMIz, WHR and Leptin level (mean±SD).**

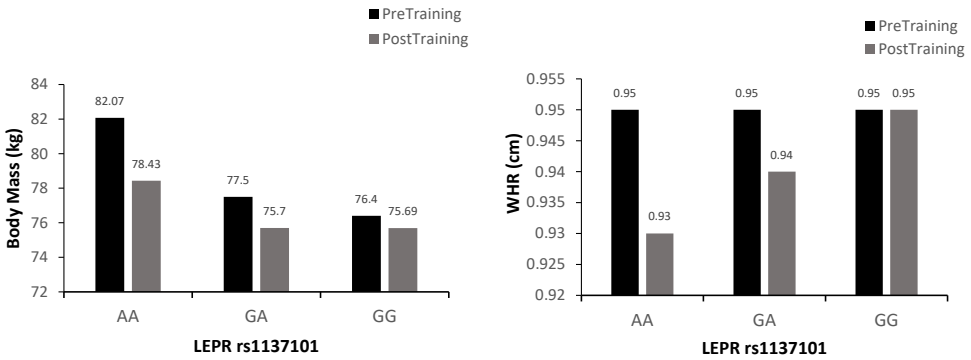

Fig. 2 **Training × genotype LEPR rs1137101 interaction for Body Mass and WHR (mean±SD).**

baseline. These results are consistent with previously published studies that reported obese people with GG homozygotes had lower leptin levels compared to those with heterozygous or homozygous for A allele.[13,27] A study by Jiang et al. predicted that *rs2167270* would change the binding site of the transcription factor and it could affect the transcription of the leptin gene.[28] Consequently, this SNP may affect gene expression at the transcription level, leading to impaired leptin production.[28] In addition, participants with G homozygous experienced a greater reduction in leptin levels in response to training which is same as previous studies.[10] In a study conducted on 242 European participants, Walsh et al. showed that individuals with GG homozygous may gain additional health benefits from expending more energy in training due to their genetic predisposition compared to carriers of the A allele.[10]

In *rs1137101* leptin receptor gene, the lowest leptin level was observed in GA heterozygous at baseline. Data on the association between polymorphism in *LEPR* gene and serum leptin levels have been observed in a number of groups; although they are contradictory. While some studies have reported the association between glutamine allele (Q) with higher serum leptin levels in plasma,[29, 30] others have found that allele arginine (R) is associated with increased leptin levels.[31, 32] At the amino acid level, this polymorphism results in a change in the electric charge from neutral to positive in this position, thereby affecting the performance of the receptor and changing its signaling capacity. In our study, both types of alleles (GG and AA) experienced a decrease in leptin in response to training, and the decrease rate was higher in homozygous AA, although these changes were not significant. Whether the regular physical activity can affect leptin production through this polymorphism needs further investigation.

Leptin has been shown to negatively regulate hepatic function of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMG-CoA) and reduce cholesterol biosynthesis.[12] Moreover, leptin positively regulates cholesterol catabolism and reduce plasma very-low density lipoprotein cholesterol levels.[33] The researchers founded that the *LEPR* polymorphism is associated with significant increase of serum TC, TG, LDL-C, and HDL-C levels in obese and non-obese individuals.[12] In our study, boys with GG genotypes (*rs1137101*) had higher TG and LDL-C and lower HDL-C levels than boys with AG and AA genotypes which is consistent with the results of other studies.[34-36] Also, boys with AA genotypes (*rs2167270*) had higher TG, TC and LDL-C and lower HDL-C levels than boys with GA and GG genotypes. Hence, our results show that the presence of the G (*rs1137101*) and A (*rs2167270*) alleles increases the risk of anthropometric and lipid abnormalities in the obese boys.

In response to 8 weeks of combined exercise in obese boys, the greatest improvement in lipid profile was observed in people with genotypes AA (*rs2167270*) and GG (*rs1137101*). To our knowledge, there is only one study that examines the interaction between leptin and leptin receptor polymorphisms and changes in lipid profile response to a training program. In a recent study by Leońska-Duniec et al., highest decrease in LDL-C was observed in young women carrying homozygous AA (*rs1137101*) following 12 weeks of aerobic exercise.[12] It is worth noting that the subjects in our study were obese boys, while the subjects studied by Leońska-Duniec et al. were young women with normal BMI. Another factor could be different type of training protocol (aerobic vs combined training).

Leptin is commonly thought to be an important hormone in reducing obesity, but studies have shown that obese people have higher leptin levels, resulting in 'leptin resistance',[37] i.e., increased production of leptin from adipose tissue that occurs in obese people leads leptin-sensitive tissues like skeletal muscle and liver to resist its effects.[38] Leptin resistance is associated with impaired leptin transport from the blood–brain barrier; hence, JAK/STAT leptin messaging will be reduced and a suppressor of cytokine-3 messaging will be induced.[39] Weakening of leptin sensitivity in the brain will result in additional accumulation of TG in adipose tissue, muscle, liver, and pancreas, ultimately leading to impaired insulin sensitivity.

Exercise plays an important role in improving leptin and insulin sensitivity. Since premature puberty in children is one of the side effects of increasing leptin levels, reducing leptin levels through reducing adipose tissue is considered as a positive effect of exercise on obese children.[40] Moreover, it improves insulin sensitivity and increases glucose transporter type 4 (GLUT4) by activating AMP-activated protein kinase and reduces leptin resistance through lowering leptin levels.[35]

The present study has a number of limitations that should be noted. First, our study consisted of exclusively male samples; therefore, the results should not be generalized to girls. Second limitation was small sample size of this study which may reduce the external validity of the research. Further studies with larger sample size in other populations are warranted.

Conclusion

Our results showed that A variant of *rs2167270* and G variant of *rs1137101* may be considered as disadvantageous factor in the context of training-induced effects on body mass traits in obese boys. Unfortunately, the results of profile lipid are inconsistent.

Practical implications

The present study provides evidence that DNA sequence variations in the *LEP* and *LEPR* genes are associated with the magnitude of the effects of regular physical activity on body mass, WHR and leptin concentration among obese boys. Therefore, the screening of polymorphisms in the *LEP* and *LEPR* as well as other genetic markers may be useful to identify individuals who are expected to respond well or poorly to exercise. As a result, the main challenge in treating obesity in the near future will be discovering the chains behind genetic communications with obesity and regular physical activity.

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Conflict of interest.

The authors declare no conflict of interest

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